

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209229Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209229
Product Name and Strength:	Lucemyra (lofexidine), 0.18 mg tablet
Applicant/Sponsor Name:	US WorldMeds, LLC
FDA Received Date:	May 7, 2018
OSE RCM #:	2017-1994-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling for Lucemyra (Appendix A) to determine if they are acceptable from a medication error perspective. US World Meds revised the container label, carton labeling, and packaging configuration to align with their current storage and stability data.

2 DISCUSSION OF REVISIONS

US World Meds revised the container label and carton labeling to align with their current storage and stability data. Data submitted by US World Meds indicated that the medication should be stored and dispensed in the original container with a desiccant and away from heat and moisture. US World Meds also revised their packaging configuration- from an (b) (4) count bottle to 36 and 96-count bottles. This revision better aligns the variable dosing regimens for Lucemyra and minimizes the number of unused tablets. See Appendix A for a comparison of the revisions and the revised container labels and carton labeling.

We discussed these revisions with DAAAP and the Office of Pharmaceutical Quality (OPQ). DAAAP and OPQ found these revisions acceptable, and we concur with their assessment.

3 CONCLUSION

The revised container label, carton labeling, and packaging configurations for Lucemyra are acceptable from a medication error perspective. We have no further recommendations at this time.

Appendix A. Side by Side Comparison of Revisions

	Previous Information: Received on July 28, 2017	Current Proposed Information: Container Label and Carton Labeling – Received May 7, 2018 Product Information – Based on current working PI as of 5/9/2018
Prescribing Information		
Indication	- mitigation of symptoms associated with opioid withdrawal - facilitation of completion of opioid discontinuation treatment.	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.
Route of Administration	Oral	Oral
Dosage Form	Tablets	Tablets
Strength	0.18 mg	0.18 mg
Dose and Frequency	Four tablets four times daily for 7 days. (b) (4) Renal and hepatic impairment require dose reductions based on the severity of impairment as follows: (b) (4) tablets (b) (4) 4 times daily.	(b) (4) three tablets four times daily for 5 to 7 days following last use of opioid. Treatment may be continued for up to 14 days with doses guided by symptoms.
How Supplied/Container Closure	(b) (4) count bottle packaged in a carton	Bottle of 36 tablets packaged in a carton Bottle of 96 tablets packaged in a carton

	Previous Information: Received on July 28, 2017	Current Proposed Information: Container Label and Carton Labeling – Received May 7, 2018 Product Information – Based on current working PI as of 5/9/2018
Storage	Room temperature	Store in original container at room temperature. Keep LUCEMYRA away from excess heat and moisture both in the pharmacy and after dispensing. Do not remove desiccant packs from bottles until all tablets are used.
Container Label	(b) (4)	(b) (4)

	Previous Information: Received on July 28, 2017	Current Proposed Information: Container Label and Carton Labeling – Received May 7, 2018 Product Information – Based on current working PI as of 5/9/2018
Carton Labeling	(b) (4)	(b) (4)

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/s/

JAMES H SCHLICK
05/15/2018

OTTO L TOWNSEND
05/15/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: May 9, 2018

To: Pamela Horn, Clinical Reviewer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Kim Compton, Regulatory Project Manager, (DAAAP)

Lisa Basham, Associate Director for Labeling, (DAAAP)

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP labeling comments for LucemyraTM (lofexidine) tablets, for oral use

NDA/BLA: NDA 209229

In response to DAAAP's consult request dated October 27, 2017, OPDP has reviewed the proposed product labeling (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA/BLA submission for Lucemyra.

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on May 3, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI/Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 7, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
05/09/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 9, 2018

To: Sharon Hertz, MD
Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): LUCEMYRA (lofexidine)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209229

Applicant: US WorldMeds

1 INTRODUCTION

On September 25, 2017, US WorldMeds submitted for the Agency's review an original New Drug Application (NDA) 209229 Rolling Submission for LUCEMYRA (lofexidine) tablets. The proposed indication for LUCEMYRA is for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on October 27, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LUCEMYRA (lofexidine) tablets.

2 MATERIAL REVIEWED

- Draft LUCEMYRA (lofexidine) tablets PPI received on September 25, 2017, and received by DMPP on May 2, 2018 and OPDP on May 3, 2018
- Draft LUCEMYRA (lofexidine) tablets Prescribing Information (PI) received on September 25, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 2, 2018 and OPDP on May 3, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
05/09/2018

LATOYA S TOOMBS
05/09/2018

LASHAWN M GRIFFITHS
05/09/2018



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 28, 2018.

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D. Acting Director
Martin S. Rusinowitz, M.D., Senior Medical Officer
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Edward Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **NDA 209229: Lofexidine Hydrochloride** tablets (0.18 mg)
Trade Name: Lucemyra
Dosages: 3 tablets QID for a total daily dose of 2.16 mg, or 4 tablets QID for a total daily dose of 2.88 mg.
IND Number: 47,857
Indication: Mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment
Sponsor: US WorldMeds
PDUFA Goal Date: May 26, 2018

Materials Reviewed:

- 1.14 Labeling
- 1.6.3 – Meeting minutes – Type B preNDA – 2015-11-16
- 2.4 Nonclinical overview
- 2.7.4 Summary of Clinical safety
- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic drug interactions
- 4.2.2 Pharmacokinetics and ADME
- 4.2.3.2 Repeat-dose toxicity
- 5.3.5.4 Abuse Potential assessment report
- 5.3.1 Reports of Biopharmaceutic Studies
- 5.3.3 Reports of Human Pharmacokinetic (PK) studies

- 5.3.4 Reports of Human Pharmacodynamic (PD) studies
- 5.3.5 Reports of efficacy and safety studies

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I. Summary

1. Background

This memorandum is in response to a consult request by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) dated October 24, 2017, to evaluate abuse-related data submitted in NDA 209229 (developed under IND 47,857) for Lofexidine Hydrochloride (HCl) tablets (0.18 mg; Trade Name: Lucemyra). Lofexidine HCl (a structural analog of clonidine) is a synthetic, selective α_2 -adrenergic receptor agonist, the binding of which reduces release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity that occurs when opioids are discontinued, removing their inhibitory effects on the system. The Sponsor is developing lofexidine immediate-release 0.18 mg tablets for treatment of opioid withdrawal symptoms and facilitation of completion of an opioid discontinuation program. Lofexidine acts centrally to suppress signs/symptoms of opioid withdrawal such as chills, sweating, stomach cramps, muscle pain, and rhinorrhea by reducing noradrenergic hyperactivity that results when the inhibitory effect of opioids is removed. Lofexidine has been marketed in the United Kingdom (UK) since 1992 by the Sponsor's licensing partner, Britannia Pharmaceuticals, Ltd., as BritLofex™ Tablets 0.2 mg (lofexidine HCl) to relieve symptoms in patients undergoing opioid detoxification.

2. Conclusions

1. Lofexidine HCl (a structural analog of clonidine) is a synthetic, selective α_2 -adrenergic receptor agonist, the binding of which reduces release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity that occurs when opioids are discontinued and their inhibitory effects on the adrenergic system removed.
2. The Sponsor is developing lofexidine immediate-release 0.18 mg tablets for treatment of opioid withdrawal symptoms and facilitation of completion of an opioid discontinuation program.
3. The nonclinical assessment of lofexidine shows that it does not bind to or activate any receptors known to have abuse potential. The Sponsor did not conduct in vivo behavioral assays to determine the abuse potential of lofexidine; however, it does not have pharmacokinetic (PK) properties associated with drugs that have abuse potential such as rapid onset and high CNS penetrance.
4. Based on the adverse event (AE) profile in clinical trials, its pharmacological similarity with clonidine [(a drug not scheduled under the Controlled Substances Act (CSA))], lofexidine's several year history of use in the United Kingdom without emergence of signals of abuse: we agree with the Sponsor that lofexidine does not warrant placement in any schedule of the CSA.

5. However, due to the occurrence of a non-abuse-related withdrawal syndrome, we recommend that lofexidine not be discontinued abruptly and that withdrawal symptoms be described in Section 5, Warnings and Precautions, of the label. Physical dependence may manifest separately from abuse liability and psychological dependence. Therefore, the occurrence of withdrawal symptoms upon discontinuation of lofexidine does not, necessarily, imply abuse potential. These withdrawal symptoms include diarrhea, insomnia, anxiety, chills, hypertension, hyperhidrosis and extremity pain.

3. Recommendations

CSS recommends the following labeling changes, where additions are indicated in bold underlined text and deletions have been stricken through:

2.1 Dosing Information

LOFEXIDINE **should not be stopped abruptly. Dose reduction should be performed gradually over a 2- to 4-day period to avoid withdrawal symptomatology.**

5 Warnings and Precautions

5.3 **Withdrawal: Instruct patients not to discontinue therapy without consulting their physician. Abrupt withdrawal of Lofexidine may lead to a withdrawal syndrome of diarrhea, insomnia, anxiety, chills, hypertension, hyperhidrosis and extremity pain. When discontinuing therapy with Lofexidine tablets, reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.**

Based on our findings we recommend the following:

- Lofexidine should not be controlled under the CSA.
- (b) (4) need not be included in the product label.

II. DISCUSSION

1. Chemistry

The chemical properties of a substance are important for an assessment of abuse potential because they can give an early indication as to the pharmacological effects, possible methods of administration, and methods of syntheses that abusers may use to abuse the drug. An evaluation of the chemical properties of lofexidine HCl and the known active metabolites of lofexidine is given below. Lofexidine HCl is a white to off white crystalline powder that is highly soluble in water and is fairly straightforward to synthesize. It does not require any controlled substance to be synthesized and does not have any similarity to a substance currently controlled under the CSA.

1.1 Substance Information

Table 1 contains the general chemical attributes of the active pharmaceutical ingredient lofexidine HCl. Lofexidine is an α_2A adrenergic receptor agonist that is similar in structure to clonidine. The main difference being that, in lofexidine, (b) (4)

(b) (4)

Table 2 contains chemical information regarding the two major metabolites of lofexidine.

Table 1 General Chemical Properties of Lofexidine HCl

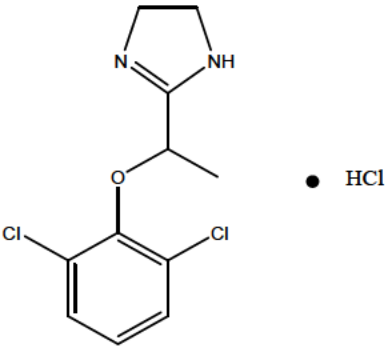
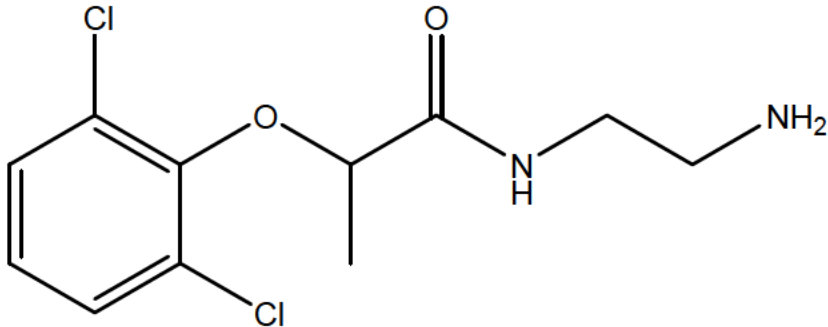
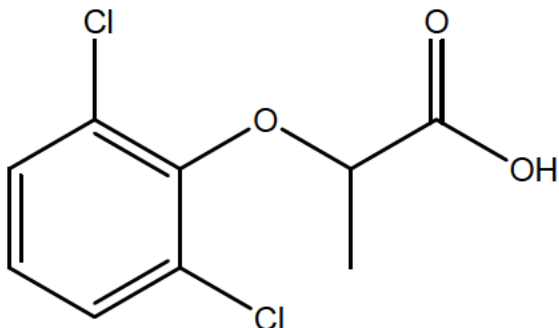
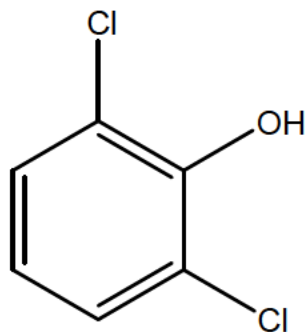
Nomenclature	
International non-proprietary name (INN)	Lofexidine
United States adopted name (USAN)	Lofexidine hydrochloride
Chemical Abstract Number (CAS)	21498-08-8
Chemical Name (IUPAC)	2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1H-imidizoline monochloride
Structure	
Molecular Formula	$C_{11}H_{13}Cl_3N_2O$
Molecular Mass	295.6 g/mol
Structure	
General Properties	
Appearance	White to off white crystalline powder
pH	5.1 (2% w/v solution)
pKa	9.43 (free base)
Solubility (25°C)	soluble: methanol and ethanol, and acidic solutions
	slightly soluble: chloroform, n-hexane, and benzene
Melting point	236°C

Table 2 Chemical properties of human lofexidine metabolites

LADP	N-(2-Aminoethyl)-2-(2,6-dichlorophenoxy)propanamide
	 $C_{11}H_{14}Cl_2N_2O_2$ MW = 277.15 g/mol
LDPA	2-(2,6-Dichlorophenoxy)propionic acid
	 $C_9H_8Cl_2O_3$ MW = 235.06 g/mol
2,6-DCP	2,6-Dichlorophenol



$C_6H_4Cl_2O$

MW = 163.16 g/mol

1.2 Product Information

Lofexidine 0.18 mg tablets will be produced as round, convex-shaped peach colored film coated tablets with the letters LFX on one side and 18 on the reverse side. The tablets will actually contain 0.175 mg of lofexidine, however, communication with the Sponsor will allow them to round up and label the tablet as 0.18 mg lofexidine (Module 1.6.3 – Meeting minutes – Type B preNDA – 2015-11-16). The composition of the tablets including excipients and their amounts are listed in table 3.

Table 3 Composition of Lofexidine Tablets, 0.18 mg

Tablet Component	Component	% w/w	Quantity (mg)	Function
(b) (4)	Lofexidine HCl ¹	(b) (4)	0.2	Active ingredient
	Lactose (b) (4)		92.6	(b) (4)
	Citric acid (b) (4)		12.3	
	Microcrystalline cellulose		5.7	
	Calcium Stearate		1.4	
	Povidone (b) (4)		1.1	
	Sodium lauryl sulfate (b) (4)		0.7	
	(b) (4)		(b) (4)	
	Opadry OY-S-9480 (b) (4)		--	
Total tablet weight (mg)			116	

¹ Provides 0.18 mg lofexidine free base per tablet

(b) (4)

None of the listed excipients are known to have abuse potential or affect the abuse potential of other substances.

2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active the Sponsor is required to determine if their active pharmaceutical ingredient, and any major metabolites, will bind to and have activity at these receptors. The Sponsor provided 4 binding and activity studies to determine the receptor binding/activity profile of lofexidine and its major metabolites. The data, summarized below, indicate that lofexidine and its metabolites, LADP, LDPA, and 2,6-DCP, do not bind to or have activity at receptors, transporters, enzymes, or ion channels tested by the Sponsor, that are known to be associated with abuse potential. The Sponsor did not conduct animal behavioral studies as part of NDA 209229.

2.1 Receptor Binding and Functional Assays

Study USWM-LX0-PHK-0010 was an in vitro binding study that tested lofexidine HCl in binding, enzyme and uptake, as well as in vitro metabolism assays. Binding is expressed as percent (%) inhibition of a radioactively labeled ligand specific for a particular target and enzyme activity is expressed as % inhibition of control enzyme activity. Generally, results showing effects (stimulation or inhibition) of $\geq 50\%$ are considered to be significant effects of the test drug. Lofexidine was tested at 10 μM against a panel of receptors and enzymes to produce the results listed in table 4. Receptors of abuse were included as part of the assay, such as opioid receptors (delta, kappa, and mu), cannabinoid receptors, (CB1 and CB2), 5-HT_{2A} receptor, and the monoamine reuptake transporters (norepinephrine, dopamine, and 5-HT). As evidenced in Table 4, lofexidine did not bind to receptors associated with abuse.

Table 4 Summary of lofexidine binding, affinity and activity

Assay	% inhibition (10 μM)	Ki (nM)	EC ₅₀ (nM)
5-HT _{1A} (h) (agonist radioligand)	98.6%	45	310
5-HT _{1B} (antagonist radioligand)	53.8%	No affinity	No activity
5-HT _{1D} (antagonist radioligand)	86.1%	513	57
5-HT _{2B} (h) (agonist radioligand)	72.2%	No affinity	88
5-HT _{2C} (h) (agonist radioligand)	95.1%	510	No activity
5-HT ₇ (h) (agonist radioligand)	82.3%	405	No activity
α_{1A} (h) (antagonist radioligand)	97.9%	287	0.76
α_{2A} (h) (antagonist radioligand)	98.6%	7.2	4.9
D _{2S} (h) (agonist radioligand)	82.3%	No affinity	No activity

This study also included the results of an in vitro metabolism assay which sought to determine the mechanism through which lofexidine was metabolized. Hepatocytes from several different species were used to determine that humans and dogs have the most similar mechanism of action to metabolize lofexidine and that this mechanism includes hydroxylation or hydroxylation and reduction of the parent drug. Further information on the metabolites of lofexidine is discussed later in this section and in Sections 2.2 and 3.1.

Further evaluation of the binding and activity of lofexidine was conducted in studies USWM-LX0-PHA-0005 and USWM-LX0-PHA-0007. The results of these studies indicated that lofexidine has high affinity for α_{2A} -adrenoceptors ($K_i = 7.2$ nM), moderate affinity for α_{1B} -adrenoceptors ($K_i = 45$ nM) and weak affinity for α_{1A} -adrenoceptors, 5-HT₇, 5-HT_{2C}, and 5-HT_{1D} receptors ($K_i = 287, 405, 510$, and 513 nM respectively). Studies on the activity of lofexidine at these particular receptors indicated that it was highly potent (agonist) at α_{2A} -adrenoceptors and α_{2C} -adrenoceptors ($EC_{50} = 4.9$ and 0.86 nM, respectively), moderately potent (agonist) on α_{2B} -adrenoceptors ($EC_{50} = 88$ nM) and 5-HT_{1D} receptors ($EC_{50} = 57$ nM) and weak agonist potency on 5-HT_{1A} receptors ($EC_{50} = 310$ nM). Lofexidine was determined to be inactive at the following receptors: 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₇, and D_{2S}. These data are summarized in Table 4. In conclusion, binding and functional assays indicate that the parent compound, lofexidine, does not bind to or have activity at receptors known to be associated with abuse potential.

Study USWM-LX0-PHA-0006 was conducted by the Sponsor to determine the in vitro binding of the metabolites of lofexidine: LADP, LDPA, and 2,6-DCP. The metabolites were tested at 10 μ M against a panel of receptors, ion channels, and transporters that included those associated with abuse potential. The only significant effect was with LADP which showed 73.4% inhibition at the serotonin transporter. Further evaluation of LADP at the 5-HT transporter (study USWM-LX0-PHA-0007) indicated that the metabolite has a $K_i = 1500$ nM which is considered very low affinity and is 750 times the steady state plasma concentration of 1.85 nM (Table 5).

Lofexidine, and its major metabolites LADP, LDPA, and 2,6-DCP, do not bind to or have activity at receptors, transporter, enzymes, or ion channels, tested by the Sponsor, that are known to be associated with abuse potential.

2.2 Safety Pharmacology/Metabolites

Studies conducted to determine the safety of a substance (and its metabolites) from therapeutic and supratherapeutic doses are extremely pertinent to drugs with abuse potential. This is because individuals with an abuse-related disorder rarely follow dosing guidelines and typically administer the substance through various methods of administration and doses to achieve the desired effects. As a result, the Sponsor conducted the following studies on lofexidine to determine the no-observed-adverse-effect level (NOAEL) of 0.3 to 1 mg/kg in dogs. This is approximately 7-fold the maximum therapeutic human dose as calculated by human equivalent dose calculations. Studies on the metabolites were not conducted by the Sponsor because the metabolites were found to not bind to, or have activity at, receptors tested in the in vitro receptor screen.

Study USWM-LX0-PHA-0001 was conducted to assess the effects of lofexidine on the outward potassium current generated by the human ether-a-go-go related gene (hERG) expressed in Chinese hamster ovary (CHO) cells. Inhibition of this channel in the heart results in a potentially fatal disorder called long QT syndrome. Lofexidine inhibited the potassium current carried by the hERG channel (I_{Kr}) at 53.44 μ g/mL of lofexidine (free base). Table 5 shows that the steady state maximum concentration of lofexidine is approximately 20 nM or $10,000$ fold lower than the dose required to inhibit the channel.

To further evaluate the cardiovascular and respiratory effects of lofexidine, the Sponsor conducted study USWM-LX0-PHA-0002. This study was conducted in Beagle dogs who were given doses of 0.3 , 1 , and

3 mg/kg lofexidine orally. No effect of the drug was measured on respiratory function, blood pressure, body weight, or mortality, however, there was a dose dependent effect on bradycardia and prolongation of the QT interval was seen at the highest dose (3 mg/kg). The pharmacokinetic measurements at the 3 mg/kg dose were determined to be: $C_{max} = 1.48 - 987$ ng/mL, $T_{max} = 3.5$ hours, and $AUC_{0-last} = 192$ ng/mL. The Sponsor thinks the range in C_{max} values is the result of emesis in dogs given the higher doses of drug.

Although it appears unlikely that this drug will be abused, it should be noted that individuals taking the drug at high doses, as individuals with drug abuse disorders are likely to do, may suffer from potentially serious cardiovascular effects such as long QT syndrome and bradycardia.

2.3 Findings from Safety Pharmacology and Toxicology Studies

The Sponsor conducted several toxicology studies. In agreement with the Agency, only repeat dose studies were submitted as part of the NDA (Module 1.6.3 – Meeting minutes- type B preNDA – 2015-11-16).

The Sponsor calculated a NOAEL in rats of 2.5 mg/kg/day and 0.88 mg/kg/day in dogs. Overall the Sponsor conducted four repeat dose studies in rats at doses ranging from 2.5 to 8 mg/kg/day. Mortality occurred at the highest doses and adverse events varied widely. There were no measurements taken upon cessation of drug administration after chronic dosing that might typically be useful for evaluating physical dependence. Therefore, it appears as though the Sponsor did not assess physical dependence in the rat.

The Sponsor conducted two repeat dose toxicity studies in Beagle dogs. Doses of 1 or 3 mg/kg/day were administered orally over the course of 90 days. A NOAEL of 1 mg/kg/day was calculated for one of the studies. However, similar to the rat studies, the Sponsor did not perform any assessments of physical dependence with these studies.

2.4 Animal Behavioral Studies

No animal behavioral studies were conducted to assess the abuse potential of lofexidine or its metabolites.

2.5 Tolerance and Physical Dependence Studies in Animals

No animals studies were conducted to determine the tolerance or physical dependence of lofexidine or its major metabolites. (b) (4)

Drugs of a similar class (e.g., clonidine) are typically tapered down over the course of 2-4 days when discontinuing use.

3. Clinical Pharmacology

The clinical pharmacology of a substance is an assessment of how that substance associates with the body and typically includes measurements of PK, pharmacodynamics, toxicology, drug interactions, and several other parameters. In the context of an abuse potential assessment, observations obtained from these studies can suggest a mechanism of action, whether or not the drug enters and has activity in

the CNS, whether the drug produces psychoactive effects, whether these observations vary depending on routes of administration, and whether there are particular properties that may impact the extent to which the drug is sought for abuse purposes (e.g. fast onset). The Sponsor did not assess these points directly, as there were no receptor binding interactions in in vitro assays or other signals of abuse potential to warrant further assessment of these parameters from an abuse perspective.

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

The Sponsor conducted several studies to assess the PK, absorption, distribution, metabolism, and elimination of lofexidine. Table 5 summarizes the PK from clinical studies of lofexidine and its major metabolites LADP, LDPA, and 2,6-DCP. In brief, the maximum therapeutic dose of lofexidine produced a C_{max} of 5.2 ng/mL at steady state, a t_{max} of 2.92 hours, with a half-life of approximately 12 hours. Similar data were generated for the metabolites; however, they were found to have little to no activity in vitro.

Table 5 Summary of Clinical Pharmacokinetics for Lofexidine and Major Metabolites (Taken from Module 2.4 Nonclinical overview, pg. 9)

Analyte	Key Parameter	Reference Values	Source(s)
Lofexidine	Steady-state C_{max} Dose A ^a [ng/mL (nM)] ^b	4.67 (18 nM), 5.2 (20 nM)	LX1-1013
	Steady-state C_{max} Dose B ^a [ng/mL (nM)] ^b	4.29 (16.6 nM)	LX1-3003-1
	t_{max} (h)	2.92	LX1-1013
	$t_{1/2}$ (h)	15.46 (Dose A), 11.25 (Dose A), 12.1 (Dose A)	LX1-1013, LX1-3003-1
LADP	Steady-state C_{max} Dose A ^a [ng/mL (nM)] ^b	0.513 (1.85 nM)	LX1-1013
	Steady-state C_{max} Dose B ^a [ng/mL (nM)] ^a	NC	
	t_{max} (h)	1.83	
	$t_{1/2}$ (h)	17.62	
LDPA	Steady-state C_{max} Dose A ^a [ng/mL (nM)] ^b	1.01 (4.33 nM)	LX1-1013
	Steady-state C_{max} Dose B ^a [ng/mL (nM)] ^b	NC	
	t_{max} (h)	2.21	
	$t_{1/2}$ (h)	17.62	
2,6 DCP	Steady-state C_{max} Dose A ^a [ng/mL (nM)] ^b	0.739 (4.53 nM)	LX1-1013
	Steady-state C_{max} Dose B ^a [ng/mL (nM)] ^a	NC	
	t_{max} (h)	2.35	
	$t_{1/2}$ (h)	42.71	

^a Dose A: 3.2 mg/day lofexidine HCl (2.88 mg/day lofexidine) administered as 0.8 mg (0.72 mg) QID; Dose B: 2.4 mg/day lofexidine HCl (2.16 mg/day lofexidine) administered as 0.6 mg (0.54 mg) QID.

^b Conversions from ng/mL to nM were calculated using the following molecular weights: 259.13 g/M, 277.15 g/M, and 233.00 g/M 163.16 g/M for lofexidine, LADP, LDPA, and 2,6 DCP, respectively)

NC = not calculated/ not evaluated; LADP = N [2'-(2,6-dichlorophenoxy-) propionyl]-1,2-diaminoethane (lofexidine metabolite); LDPA = 2-(2',6'-dichlorophenoxy) propionic acid (lofexidine metabolite)

Absorption of lofexidine was measured using both in vitro and in vivo assays. The in vitro assay determined that at up to 1 μ M of lofexidine was not a substrate for P-glycoprotein (P-gp) transporters. In vivo absorption was measured through the injection of radiolabeled lofexidine in rats, dogs, and monkeys (studies USWM-LX0-PHK-0001 and USWM-LX0-PHK-0002). The overall results of these studies indicate that lofexidine is rapidly absorbed (1.5 hrs in rats, 2 hrs in monkeys, and 2-4 hrs in dogs). Sex-dependent effects on the rates of absorption were seen in dogs; however, it is unknown if the differences transfer to humans.

Distribution was also measured in the in vivo radio labeled studies previously mentioned for absorption (studies USWM-LX0-PHK-0001 and USWM-LX0-PHK-0002). Rats, dogs, and monkeys were given single doses of radiolabeled drug and sacrificed at specific time points up to 120 hours, tissues were then collected and analyzed. The majority of drug was detected in the gastrointestinal tract, kidney and liver. The plasma contained higher concentrations of the drug than the surrounding tissues; however, lofexidine was detected in the brain. Approximately 60-70% of the lofexidine was determined to be bound to plasma proteins (USWM-LX0-PHK-0005).

Metabolism of lofexidine was determined using both in vitro and in vivo assays. Single oral doses of radiolabeled lofexidine was given to rats, rabbits, and dogs (USWM-LX0-PHK-0003). The primary metabolite, LADP, was measured at approximately 5% and LDPA and 2,6-DCP were measured in smaller quantities and were species dependent. An in vitro study (USWM-LX0-PHK-0009) determined that the CYP2D6 enzyme was the major contributor to the metabolism of lofexidine through oxygenation of the imidazole ring and further dehydrogenation.

The same studies were used to measure the excretion of drug in rats, dogs, and monkeys. Single doses of radiolabeled lofexidine produced determined that 50% was excreted in the urine and 30% in feces in rats. In dogs, the amount excreted in the urine was higher, at approximately 70%. In monkeys, 65% of the drug was excreted in the urine.

3.2 Drug/Product Interactions

The majority of individuals with a drug abuse disorder use multiple drugs to achieve their desired high and effect. As a result, the importance of determining drug-drug interactions between lofexidine and potentially abused drugs is of great importance for the safety of the individual in this indicated population.

The Sponsor conducted two studies in rats to determine the interaction of orally administered lofexidine with cocaine administered intraperitoneally(i.p.). Lofexidine was given at doses of 0.33 or 1.65 mg/kg followed by saline or cocaine at doses of 10, 20, 60 mg/kg. Tremors and ataxia were noted at combinations of low doses of both drugs while higher doses resulted in several fatalities. The second study conducted in beagle dogs did not have observable effects. (b) (4)

4. Clinical Studies

The lofexidine HCl clinical development program consists of healthy volunteers or opioid-dependent subjects enrolled in 16 Phase 1 studies and 4 Phase 2 studies, and in 4 Phase 3 studies that evaluated

lofexidine HCl in opioid-dependent subjects undergoing opioid withdrawal. Throughout the lofexidine development program, reports reference the 0.2 mg of lofexidine HCl salt dosage form. All studies are reported in terms of exposures to the calculated salt content. The free base molecular weight conversion requires application of a correction factor of 1.14, thus naming and labeling of lofexidine doses on the basis of the active moiety would result in describing tablet strength as 0.175 mg of lofexidine. As discussed at the pre-NDA meeting on September 24, 2015, the Division agreed that 0.175 mg could be rounded to 0.18 mg for purposes of labeling.

4.1 Adverse Event Profile Through all Phases of Development

The incidence of treatment emergent adverse events (TEAEs) was summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tables 6 and 7 show the abuse related AEs in Phase 1 studies of Lofexidine

Table 6 Abuse related adverse events in Phase 1 studies of Lofexidine

<u>Study</u>	<u>Somnolence</u>	<u>Euphoric mood</u>
LX1-1003	7/12 (58.3%)	0/12
LX-1003-1	1/6 (16.7%)	1/6 (16.7%)
LX1-1004	5/13 (38.4%)	0/13
LX0-1001	0/2	0/2
LX1-1002	27/31 (87%)	0/31
LX1-1013	9/10 (90%)	0/10
LX1-1007	2/24 (8.3%)	0/24
LX1-1008	2/16 (12.5%)	0/16
LX1-1012	1/23 (4.3%)	0/23
LX1-1005-1	6/6 (100%)	0/6
LX1-1009	11/24 (45.8%)	0/24
LX1-1010	5/24 (20.8%)	0/24
LX1-1011	10/12 (83.3%)	0/12

Numerator represents no of individuals with AE and denominator total no of individuals in the study

Table 7 Abuse related adverse events in Phase 1 studies of Lofexidine and placebo

<u>Study</u>	<u>Placebo: Somnolence</u>	<u>Lofexidine: Somnolence</u>
LX1-1005-2	3/7 (42.8%)	12/19 (63.2%)
LX1-1006	1/6 (16.7%)	14/24 (58.3%)

Numerator represents no of individuals with AE and denominator total no of individuals in the study

Phase 2 and 3 studies

An Open Label Safety Evaluation of Lofexidine for the Treatment For Opiate Withdrawal (Phase 2) USWM-LX1-2001

The main objective of these 3 related studies (Initial Study, Pilot 1, and Pilot 2) was to evaluate the safety/tolerability of lofexidine, in opiate-dependent subjects at lofexidine HCl doses of 1.6, 2.4, and 4.0 mg/day (Initial Study) and 3.2 mg/day (Pilot 1 and Pilot 2). Adults aged 21 to 59 years who were dependent on heroin, morphine, or hydromorphone were recruited. Drowsiness was noted in 33% of subjects on lofexidine dose 1.6-2.4 mg/day and 80-100% subjects on doses of 3.2-4mg/day

Evaluation of the Efficacy and Safety Profiles of Lofexidine Hydrochloride in the Treatment of Opiate Detoxification in Opiate -Dependent Patients (Phase 3) USWM LX1-3001

The primary objective was to compare the efficacy of lofexidine HCl to that of placebo in the treatment of opioid detoxification.

The secondary objectives were to assess the safety profile, treatment retention, and PK profile of lofexidine in the treatment of opioid detoxification in opioid-dependent subjects.

This was a randomized, multicenter, double-blind, placebo-controlled, multiple-dose, parallel-group study. There were 3 major phases: Phase I (Days 1-3, morphine stabilization), Phase II (Days 4-8, lofexidine/placebo treatment), and Phase III (Days 9-10, placebo treatment). Baseline safety and efficacy assessments were performed on Days 1-3. Subjects were randomized to receive either lofexidine or placebo on Day 4; lofexidine subjects received 0.8 mg QID on Days 4-7 and 0.4 mg QID on Day 8. All subjects received placebo on Days 9 and 10. Male and female opioid-dependent subjects (opioid use in 21 out of previous 30 days) were enrolled. Sixty eight (68) subjects were randomized to study medication on Day 4; Thirty-five (35) subjects were randomized to receive lofexidine and 33 subjects were randomized to receive placebo. No abuse related AEs were reported.

A Phase III, randomized, multicenter, double blind placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in subjects undergoing opiate detoxification USWM LX1-3002

The primary objective was to investigate the efficacy of lofexidine hydrochloride in reducing withdrawal symptoms in subjects undergoing opioid detoxification. This was an inpatient, randomized, multicenter, double-blind, placebo-controlled, parallel group study of the clinical efficacy and safety of lofexidine in subjects with opioid dependence and experiencing withdrawal. This was an 8-day study consisting of 3 phases: Phase I (Screening); Phase II (Days 1 -5) where subjects were admitted to an inpatient unit and randomized to receive either lofexidine (0.8 mgQID or placebo QID after the baseline assessments were performed on Day 1, and Phase III (Days 6-8) where all subjects received placebo QID on Days 6 and 7. Two hundred and sixty four (264) subjects were randomized to study medication and received at least one dose of study medication. Eighty five subjects completed the study. No discontinuation occurred due to abuse related AEs . Somnolence occurred in 13 of 134 (9.7%) lofexidine treated subjects and 6 of 130 (4.6%) placebo treated subjects. Sedation occurred in 8.2 percent lofexidine and 1.5% placebo treated subjects.

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the treatment of Opioid Withdrawal (Days 1 to 7) Followed by Open-Label, Variable-Dose Lofexidine Treatment (Days 8 to 14) USWM-LX1-3003-1

This Phase 3, multicenter study was completed in two parts. Part 1 of the study (Days 1 to 7) used an inpatient, randomized, double-blind, placebo-controlled design. Subjects were randomized to receive lofexidine HCl 2.4 mg/day, lofexidine HCl 3.2 mg/day, or placebo. Part 2 (Days 8 to 14) used an open-label, variable-dose design to capture longer-term exposure in subjects requiring lofexidine treatment beyond Day 7. Subjects who completed Part 1 were eligible to participate in the open-label phase (Days 8 to 14), during which subjects received variable-dose lofexidine HCl treatments (not to exceed 3.2 mg/day). Of the 929 subjects screened, 603 were randomized and included in the ITT population. A total of 225 subjects (37.3%) completed the double-blind phase of the study: 42 in the placebo group, 95 in the lofexidine HCl 2.4 mg/day group, and 88 in the lofexidine HCl 3.2 mg/day group. A total of 83 subjects received at least 1 dose of lofexidine drug during the open-label phase and 70 completed the open-label phase. During the double blind phase Sedation and Somnolence occurred in 5% of the placebo group (8/151) and 12% of lofexidine group (56/451).

A Phase 3, Open-Label, Safety Study of Lofexidine USWM-LX1-3003-2

The primary objective of the study was to continue to investigate the safety of lofexidine HCl when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. This was a Phase 3, multicenter, open-label study of 7 days of mandatory lofexidine treatment and optional lofexidine treatment for up to an additional 7 days (no more than 14 days total). Any opioid-dependent subject seeking treatment for partial or total withdrawal from current opioid that would likely require 7 days of lofexidine treatment was eligible to participate.

A total of 286 subjects received at least 1 dose of lofexidine HCl and 168 subjects completed the study. Sedation was noted in 46/286 (16.1%) and somnolence was noted in 21/286 (7.3%) subjects.

Table 8 shows the abuse related AEs in Phase 3 studies of Lofexidine

Table 8 Abuse related adverse events in Phase 3 studies of Lofexidine and placebo: (LX1-3001, LX1-3002, LX1-3003-1[DB Phase])

	Lofexidine n=619	Placebo n= 313
Somnolence	74 (12%)	12 (3.8%)
Sedation	63 (10.2%)	9 (2.9%)

The Sponsor has not conducted a human abuse potential study on lofexidine. In the efficacy and safety Study LX1-3001, in patients undergoing opioid detoxification, visual analog scale (VAS) for feeling high (VAS-High) and Addiction Research Center Inventory Morphine Benzedrine Group (ARCI-MBG) were assessed once daily from Days 1-10. Days 1-3 were morphine lead-in (no lofexidine HCl or placebo treatment), Days 4-8, lofexidine/placebo treatment, Days 9-10, placebo treatment. Subjects in the lofexidine HCl group received 3.2 mg/day on Days 4-7, 1.6 mg on Day 8, and placebo on Days 9-10.

No statistically significant differences between treatment groups were noted for VAS-High in the mean changes from baseline.

On Days 4 through 8, the percentage of ARCI-MBG true responses was numerically greater for lofexidine than for placebo. However, the sample size was small in this latter part of the study, particularly for placebo (N= 5 to 8), and data should be interpreted with caution. Additionally, subjects were withdrawing from opioids at this time and this may affect the results on this scale.

CSS consulted the Office of Biostatistics to evaluate this study (Liu, Wei DARRTS February 16, 2018). They concluded that the study was not appropriately designed for data collection of the abuse potential endpoint VAS high. (b) (4)

However, CSS is of the opinion that the rest of the clinical and non clinical data do not provide evidence for lofexidine having abuse potential. (b) (4)

4.2 Safety Profile

The Sponsor has not conducted studies specifically addressing the abuse potential of lofexidine. They have captured abuse-related AEs during Phase 1, 2, and 3 studies. AEs were summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). In phase 3 studies, no events of euphoric mood, elevated mood, feeling drunk, or feeling/thinking abnormal were observed. Psychotomimetic effects, such as hallucinations, were observed infrequently in both lofexidine and placebo-treated subjects.

Sedative-related AEs of somnolence, sedation and fatigue were relatively common (>10.0% of patients) and were observed with a higher incidence in lofexidine-treated patients compared with placebo. Lethargy was less common but observed with a slightly higher incidence relative to placebo. Drowsiness has been reported in 33% and sedation in 10% of clonidine treated subjects (Catapres; clonidine HCl PI). In the absence of euphoria related AEs, the occurrence of somnolence and sedation does not suggest abuse potential.

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Cases of abuse, misuse, or diversion (intentional or unintentional) of lofexidine during clinical trials were recorded as AEs. However, there were no AEs reported with lofexidine that indicated abuse, misuse, or diversion in any of the studies conducted by the Sponsor.

4.4 Tolerance and Physical Dependence Studies in Humans

A single-blind placebo washout was included in 2 safety and efficacy studies of lofexidine in opioid-dependent subjects, in order to evaluate potential discontinuation effects of lofexidine. Diarrhea, insomnia, anxiety, chills, hypertension, hyperhidrosis, and pain in extremity were noted during withdrawal more commonly with lofexidine than placebo. Clinically, abrupt withdrawal of clonidine, which is similar to lofexidine, may result in a rapid increase of systolic and diastolic blood pressure with associated symptoms such as nervousness, agitation, restlessness, anxiety, insomnia, headache, and sweating. These symptoms may be related to both the increases in blood pressure, as well as other effects of rebound sympathetic overactivity.

Physical dependence may manifest separately from abuse liability and psychological dependence and the occurrence of withdrawal symptoms upon discontinuation of lofexidine does not, necessarily, imply abuse potential.

5. Regulatory Issues and Assessment

The Sponsor requests that lofexidine not be placed in any schedule of the CSA. Based on lofexidine's pharmacological similarity with clonidine as shown by receptor binding/functional studies as well as in vivo studies, on the AE profile in clinical trials, and lofexidine's several year history of use in the United Kingdom, without emergence of signals of abuse, we agree with the Sponsor that lofexidine does not warrant placement in any schedule of the CSA. (b) (4)

However, due to the occurrence of a non-abuse-related withdrawal syndrome, we recommend that lofexidine not be discontinued abruptly and that withdrawal symptoms be described in Section 5 of the label. (b) (4)

6. Other Relevant Information

Post marketing data analyzed by the Sponsor

Lofexidine has been available as an unscheduled substance in the United Kingdom (UK) since 1992 and post-market data are available. No cases of lofexidine abuse, diversion, or dependence were identified in their Periodic Safety Update Reports (PSURs), medical literature, public sources in the UK for drug abuse monitoring, the scientific literature, or World Health Organization (WHO) Vigibase®. There are reports of individuals using clonidine to self-treat opioid withdrawal (68%), feel drowsy (59%), relax (36%), "get a nod" (32%), or "boost" methadone effects (31%). The primary reasons reported for non-medical use of clonidine were to prolong/enhance effects of opioids or benzodiazepines, improve opioid withdrawal symptoms when opioids were not available, and for sedative effects.

CSS review of scientific literature did not reveal evidence of lofexidine abuse.

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/s/

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03/28/2018

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04/04/2018

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Full Review Template version: September 5, 2017

COA ID	C2017295
NDA #	209229
Referenced IND for NDA/BLA	47857
Established Name/Trade Name	Lofexidine
Applicant	US World Meds
Indication	Mitigation of symptoms associated with opioid withdrawal; facilitation of completion of opioid discontinuation treatment
Meeting Type/Deliverable	NDA Review
SDN #	1
Date of Consult Request	September 25, 2017
Review Completion Date	March 20, 2018
Review Division	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Clinical Reviewer	Pamela Horn, MD
Review Division PM	Kimberly Compton
COA Reviewer	Nikunj Patel, PharmD
Secondary Reviewer	Elektra J. Papadopoulos, MD, MPH
COA Associate Director	Elektra J. Papadopoulos, MD, MPH
Instrument 1	Short Opiate Withdrawal Scale – Gossop (SOWS-Gossop)
Instrument 2	
Instrument 3	
COA Type 1 and Endpoint Concepts	Patient-Reported Outcome: Disease-specific symptoms
COA Type 2 and Endpoint Concepts	
COA Type 3 and Endpoint Concepts	
Intended Population	Adult patients (≥18 years) who are undergoing opioid withdrawal
Internal Meeting	Not applicable
Sponsor Meeting/WRO	Not applicable

Please check all that apply:

☐ Rare Disease/Orphan Designation

☐ Pediatric

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 209229

Lofexidine

SOWS-Gossop (sx)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) regarding NDA 209229. The Applicant is seeking a FDA approval for lofexidine oral tablets for the proposed indication of *(1) mitigation of symptoms associated with opioid withdrawal and (2) facilitation of completion of opioid discontinuation treatment in adult patients (≥18 years) who are undergoing opioid withdrawal*. The Applicant completed two phase 3, randomized, double-blinded, placebo-controlled, multi-center clinical trials (USWM-LX1-3002 and USWM-LX1-3003-1) to assess safety and efficacy of lofexidine to support its marketing application. In both clinical trials, the Short Opiate Withdrawal Scale (SOWS)-Gossop, a patient-reported outcome (PRO) instrument, was used to assess short-acting opioid withdrawal symptoms in order to support corresponding co-primary/primary endpoints. Refer to the Appendix A for a copy of the SOWS-Gossop instrument.

The review division consulted the COA Staff to review relevant supportive evidence of the SOWS-Gossop as an instrument to assess symptoms of opioid withdrawal in the target patient population in support of the proposed indication. Of note, during the clinical development program, the COA Staff commented on strengths and limitations of the SOWS-Gossop in the target patient population.¹ Previous COA reviewers identified various limitations of the instrument, most notably an omission of certain relevant symptoms associated with short-acting opioid withdrawal (e.g., nausea, vomiting, diarrhea).

The COA review concludes the followings:

- The SOWS-Gossop instrument appears to assess some relevant short-acting acute opioid withdrawal symptoms (e.g., aches and pain, insomnia/problem sleeping). However, the SOWS-Gossop omits evaluation of several short-acting opioid withdrawal symptoms that are considered relevant and meaningful and described as some of the most severe acute withdrawal symptoms by patients (e.g., nausea, vomiting, diarrhea) as evidenced by the qualitative patient interviews.
- The SOWS-Gossop evidence of psychometric properties (reliability, construct validity, and ability to detect change) generally appeared supportive.
- This reviewer recommends the review division to submit an information request to the Applicant for additional data (e.g., item level analysis) to better characterize the SOWS-Gossop instrument and overall total score interpretation. While the Applicant proposed SOWS-Gossop total score as part of the co-primary/key secondary endpoints, individual item level data should be evaluated to ensure consistent improvement is being observed at the item level and that no single item is influencing the overall score change.

¹ AT 2010-101 IND 47857, Papadopoulos; AT 2012-098 IND 47857, Papadopoulos; AT 2015-149 IND 47857, Choudhry

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Nikunj Patel, PharmD

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Lofexidine

SOWS-Gossop (sx)

- Refer to Appendix B for a copy of the information request sent to the Applicant on February 6, 2018 (DARRTS Reference ID 4218924). Refer to Clinical and Statistical reviews for additional presentation and analyses of SOWS-Gossop data.

Future Clinical Development in Opioid Withdrawal:

- Recommend including a more comprehensive assessment of relevant, meaningful and most severe/important symptoms (including gastrointestinal symptoms such as nausea, vomiting, diarrhea) in the target patient population based on patient input. Sponsors should elicit patient input to confirm PRO item content comprehensiveness, relevance and importance as well as patient understanding.
- PRO instrument's instructions including the recall period should be appropriate, clear, and easy to understand for patients to validly provide recall of the information requested and complete the instrument as intended.
- Recommend appropriate translation and cultural adaptation of the PRO instrument for use in multi-national clinical trials.
- Sponsors should consider electronic administration of the PRO instrument to improve data quality and patient compliance.
- Engage FDA early and throughout drug development to ensure the development and implementation of fit-for-purpose clinical outcome assessments.

B. BACKGROUND

Materials reviewed:

- Clinical study reports for the phase 3 clinical trials (1) USWM-LX1-3002 and (2) USWM-LX1-3003-1
- AT 2010-101 IND 47857, Papadopoulos
- AT 2012-098 IND 47857, Papadopoulos
- AT 2015-149 IND 47857, Choudhry

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The clinical trial population included adult patients (≥ 18 years) who are undergoing short-acting opioid withdrawal. Refer to Clinical review for more information on clinical trial population.

Select Inclusion Criteria:

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Lofexidine

SOWS-Gossop (sx)

1. Be a male or female at least 18 years of age.
2. Have current dependence, according to the Mini International Neuropsychiatric Interview (MINI), on any opioid with a half-life similar to heroin or morphine.
3. Be seeking treatment for opioid dependence.
4. Have a score of ≥ 2 on the Objective Opiate Withdrawal Scale (OOWS-Handelsman) at baseline.

Select Exclusion Criteria:

1. Be a female subject who is pregnant or lactating.
2. Have self-reported use of methadone or buprenorphine in the past 14 days.

1.2 Clinical Trial Design

The Applicant conducted two phase 3, randomized, double-blind, placebo-controlled, multi-center, clinical trials to evaluate safety and efficacy of lofexidine. The two clinical trials were (1) USWM-LX1-3002 and (2) USWM-LX1-3003-1. In each study lofexidine was administered orally daily during the treatment period (Treatment periods: 5 days in USWM-LX1-3002; 7 days in USWM-LX1-3003-1). Of note, the USWM-LX1-3003-1 also evaluated dose-response along with safety/efficacy. A total of 264 patients were randomized in the USWM-LX1-3002 clinical trial based on 1:1 ratio (Lofexidine 2.88 mg/day arm N=134; Placebo arm N=130). Lofexidine total daily dose of 2.88 mg was administered as 0.72 mg four times daily. A total of 603 patients were randomized in the USWM-LX1-3003-1 clinical trial based on 3:3:2 ratio (Lofexidine 2.16 mg/day N=230; Lofexidine 2.88 mg/day N=222; Placebo N=151). Lofexidine total daily dose of 2.16 mg was administered as 0.54 mg four times a day. Similarly, lofexidine total daily dose of 2.88 mg was administered as 0.72 mg four times daily.

Refer to Clinical and Statistical reviews for additional background on clinical trial design.

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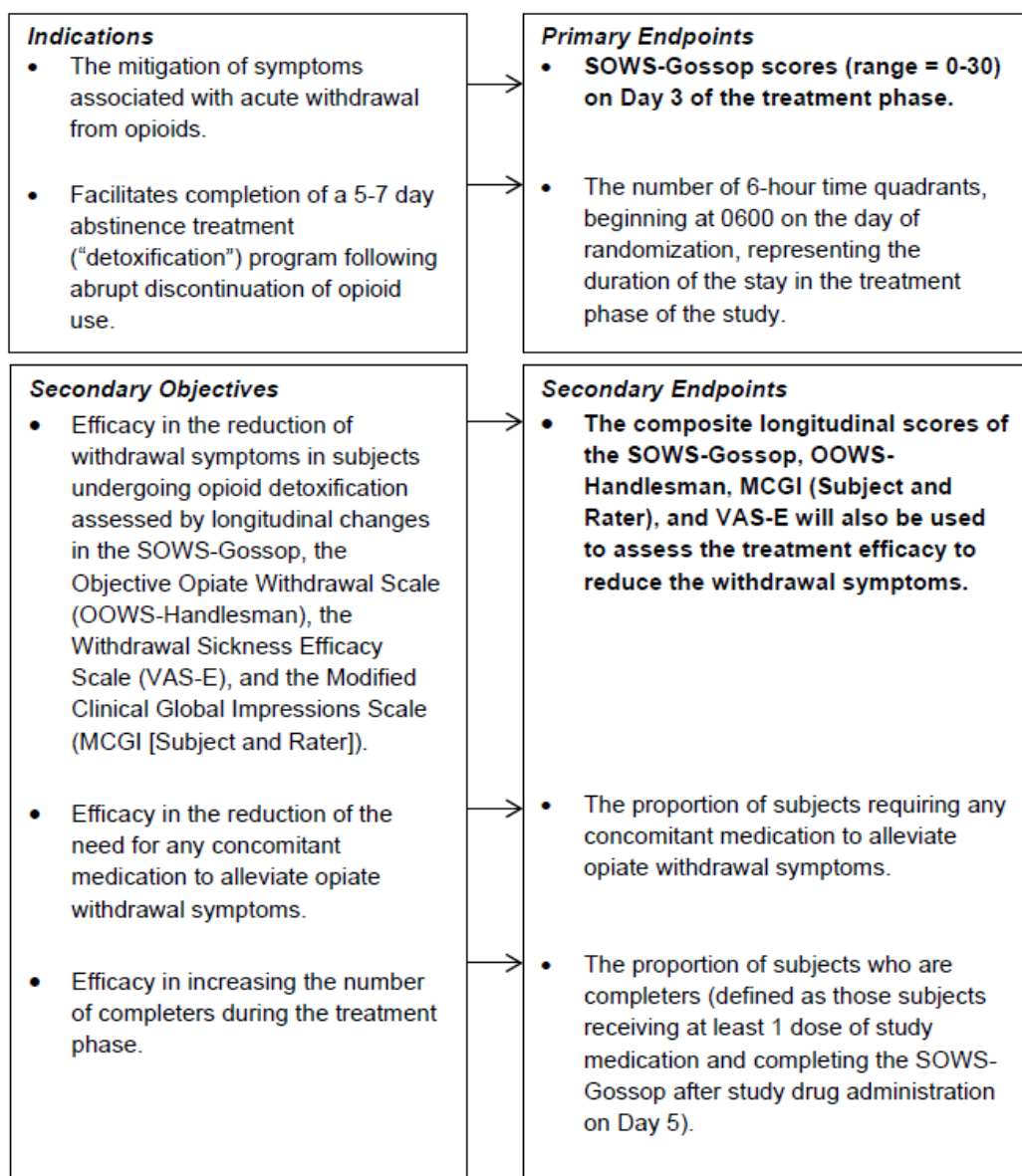
Lofexidine

SOWS-Gossop (sx)

1.3 Endpoint Hierarchy and Definitions

The Figure 1a and 1b below show endpoint hierarchy and definitions. Refer to Clinical and Statistical reviews for additional analyses of clinical trial design and endpoints.

Figure 1a. Endpoint Model for Study USWM-LX1-3002



*Note: **Bolded** endpoints are evaluated using the SOWS-Gossop*

Clinical Outcome Assessment Review

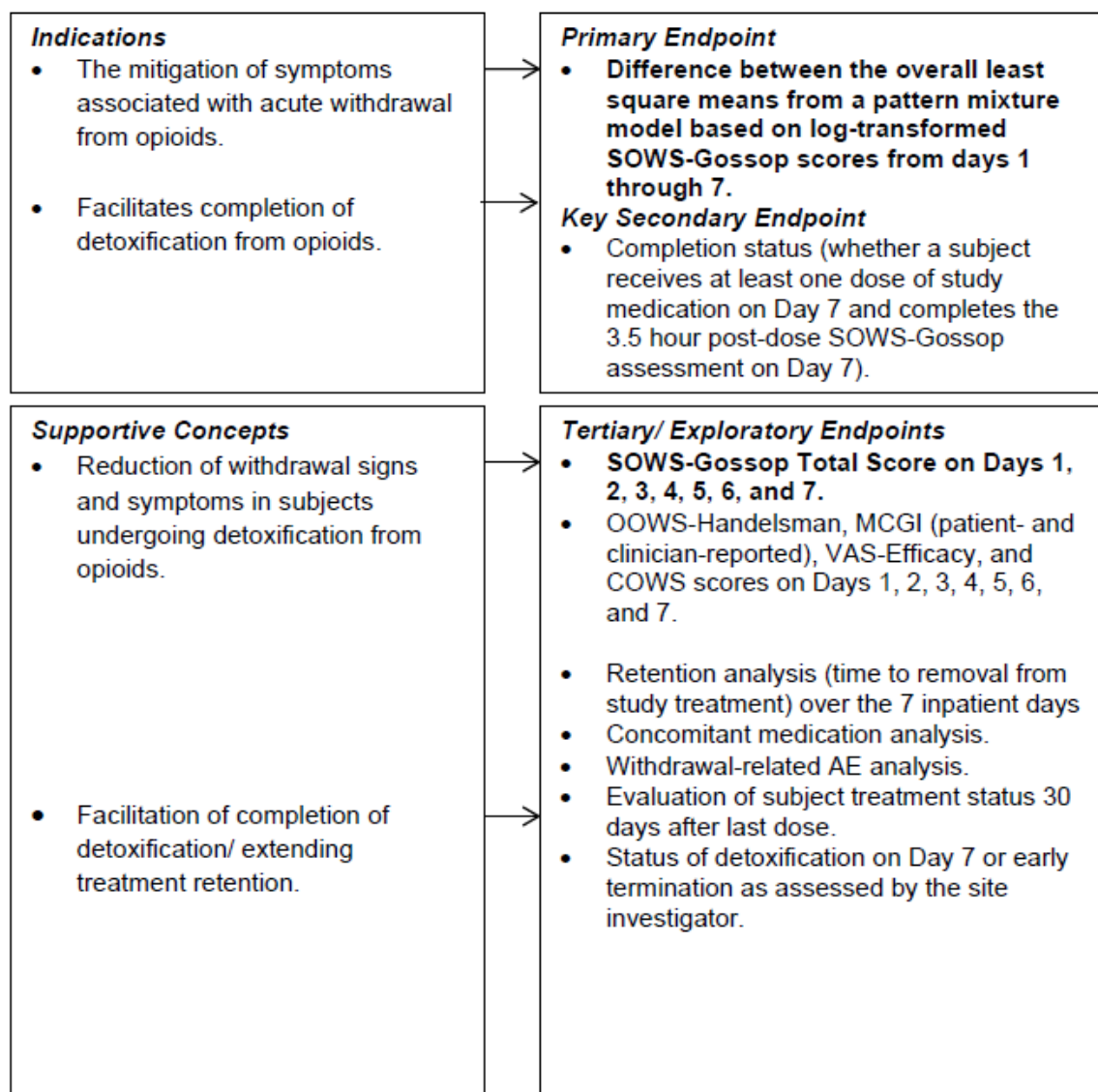
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Lofexidine

SOWS-Gossop (sx)

Figure 1b. Endpoint Model for Study USWM-LX1-3003-1



*Note: **Bolded** endpoints are evaluated using the SOWS-Gossop*

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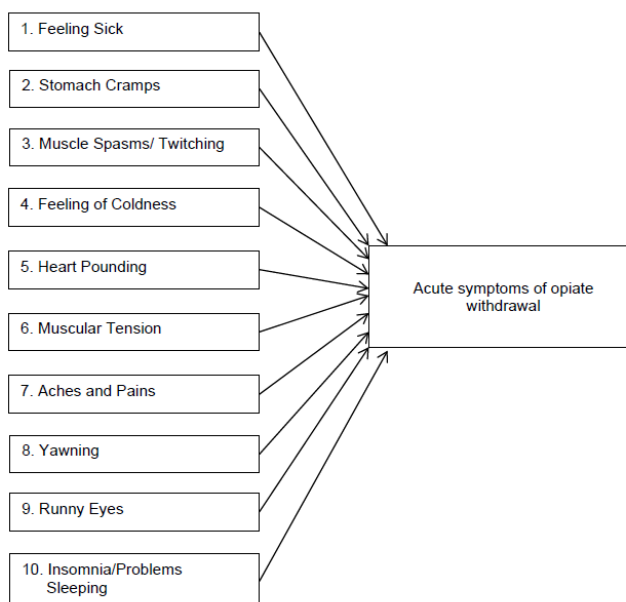
Lofexidine

SOWS-Gossop (sx)

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The Figure 2 below shows SOWS-Gossop conceptual framework provided by the Applicant.

Figure 2. Conceptual Framework of the SOWS-Gossop



(Source: PRO Evidence Dossier, Page 11)

Reviewer Comments: Refer to Section C5 Content Validity for discussion on concepts being assessed by the SOWS-Gossop in the target patient population.

3 CLINICAL OUTCOME ASSESSMENT(S)

Short Opiate Withdrawal Scale (SOWS)-Gossop: The SOWS-Gossop is a 10-item PRO instrument designed to evaluate short-acting opioid withdrawal symptoms (acute opioid withdrawal symptoms). Each item represents a symptom. Patients evaluate the severity of each symptom by placing a mark next to each item in a column entitled, “None,” “Mild,” “Moderate,” or “Severe.” Higher scores indicate more severe withdrawal response as reported by the patient. While the SOWS-Gossop was developed with a recall period of 24-hour, the Applicant appeared to have modified the recall period. The following recall period and corresponding instructions were provided to patients when completing the SOWS-Gossop once daily 3.5 hours after the first study medication dose: “Please put a check mark in the appropriate box if you have suffered from any of the following conditions during baseline or since the last time you completed this test.” Refer to Appendix A for a copy of the instrument.

Prior versions: The SOWS-Gossop scale was derived directly from the Opiate Withdrawal Scale (OWS) to simplify the assessment for patients and to eliminate redundancy. Refer to the SOWS-Gossop PRO Evidence Dossier for additional information on prior versions.

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User manual: The Applicant stated that there is no developer-written user manual for the SOWS-Gossop.

Timing, data collection method, and mode of administration: The SOWS-Gossop instrument was self-administered once daily at baseline and throughout the duration of two clinical trials using paper-based method. The SOWS-Gossop was to be completed at 3.5 hours after administration of the initial study medication dose of the day.

***Reviewer Comment:** The Applicant assessed symptom severity at the time of peak plasma concentration of lofexidine, which was 3.5 after initial study medication dose of the day.*

Training method/materials: The Applicant provided training materials to patients and administrators. Refer to the PRO evidence dossier for additional background.

4 SCORING ALGORITHM

The SOWS-Gossop is scored by summing or averaging scores obtained for the 10 individual items ranging from 0 to 3 (None = 0, Mild = 1, Moderate = 2, and Severe = 3) with a total possible score range from 0 to 30 and a total possible average score ranging from 0 to 3. A higher score indicates a greater withdrawal symptom severity. An average score of 1 would indicate that the patient is experiencing Mild withdrawal, 2, Moderate withdrawal, and 3, Severe withdrawal.

In the lofexidine clinical trials (USWM-LX1-3002 and USWM-LX1-3003-1), the SOWS-Gossop was scored using a sum of the 10 individual symptom scores, with possible total scores ranging from 0 to 30.

5 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☐ Documentation of expert input
- ☒ Qualitative study protocols and interview guides for focus group or patient interviews
- ☒ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☒ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
- ☐ Qualitative support for meaningful change
- ☒ Quantitative study summary with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Content validity is defined and supported by qualitative research (e.g., literature review, patient interviews, experts input) that demonstrates that the COA instrument measures the concept of interest (e.g., disease related signs and symptoms) including evidence that the item content of an

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instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties generally does not replace or rectify problems with content validity.

Dr. Yasmin Choudhry reviewed the SOWS-Gossop instrument's content validity evidence, previously submitted during the IND phase. The same evidentiary documentations were re-submitted in the current NDA 209229 submission. Note that the results of qualitative research were not reviewed by FDA before the SOWS-Gossop was utilized in phase 3 trials. Refer to AT 2015-149 IND 47857 for an in-depth review. This reviewer summarizes key elements of Dr. Choudhry's review below.

- The Applicant conducted literature review, and concept elicitation and cognitive interviews in 20 adult patients (n=20) undergoing short-acting opioid withdrawal symptoms. No expert input was sought.
- Qualitative study patients were males or females (≥ 18 years), having experienced dependence within 45 days of screening, having voluntarily sought treatment for opioid dependence within 45 days of screening, and having experienced acute, unassisted withdrawal from short-acting opioids within 45 days of screening.
 - The mean time since the participants' substance related disorder diagnosis was about 2.5 weeks with a range of 0 to 3.4 months since diagnosis.
 - Participants were required to have experienced unassisted withdrawal for at least 3 days; efforts were made to recruit at least 5 participants who had experienced unassisted withdrawal for at least 7 days.
 - All 20 patients reported experiencing acute, unassisted withdrawal for at least three days, with a range of 3-12 days. Forty percent of the participants experienced acute, unassisted withdrawal for at least seven days, with a range of 7-12 days.
 - The mean (SD) duration of substance related disorder was 7 (4.4) years with a range of approximately five months to 17 years.
 - Comorbid conditions included anxiety disorder (n=10; 50%) and depression (n=10; 50%).
- Symptoms that occurred almost immediately in the first days of withdrawal were reported to include runny nose, watery eyes, fatigue, and body aches and pains. These were described as quickly and steadily worsening in intensity over the first 1-2 days of withdrawal.

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- The second, third, and fourth day were described as the worst, most severe symptoms days. Participants commonly reported experiencing vomiting, diarrhea, muscle spasms, difficulty sleeping, restless legs, feelings of cold/shivering. The severity of symptoms on the worst day was often described as a 9, 10, or 11 on a scale of 1-10, where 1 represented least severe and 10 represented most severe.
- Participants reported that symptoms continued during the days after the worst day, including aches and pains, fatigue or low energy, weakness, runny nose, and yawning.
- Dysphoria and anxiety were also reported and became more prominent as physical symptoms diminished. Participants reported that even though physical symptoms had gone away after one week of withdrawal, they continued to have physical and psychological opiate cravings.
- As symptoms gradually improved, participants reported beginning to have an appetite/able to eat food, gastrointestinal symptoms diminishing, and being able to sleep for a few hours at night. Finally, one week after withdrawal many symptoms were reported to have disappeared; however, some participants reported continued fatigue and low energy, weakness, aches and pains, and emotional symptoms.
- Regarding the “feeling sick” item, most participants described “feeling sick” as nausea, vomiting, diarrhea, flu-like symptoms, cannot get out of bed, unwell, body aches, not feeling normal, or fever upon probing. Other descriptions included: no energy, exhausted, fatigue, no motivation, sweating, loss of appetite, dehydration, feeling like stuff was crawling all over me.
- Response options were generally well understood by the participants.
- A recall period of 24-hour was generally supported and appeared optimal to capture the severity of symptoms. Of note, the Applicant utilized slightly modified recall period instruction.

Refer to AT 2015-149 IND 47857, AT 2010-1010 IND 47857, and AT 2012-098 IND 47857 for past COA comments by Drs. Yasmin Choudhry and Elektra Papadopoulos.

***Reviewer Comments:** The SOWS-Gossop instrument appears to assess some relevant and important patient-reported symptoms associated with short-acting opioid withdrawal in acute setting as evidenced by the Applicant’s qualitative patient interviews and confirmation by the clinical reviewer; however, there are some limitations related to comprehensiveness of the included symptoms and clarity of instructions (e.g., recall period, terminology) in the target patient population.*

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Acute withdrawal symptoms such as aches and pain, feeling cold, sleeping difficulty, muscle twitching or spasms, and stomach cramps were commonly endorsed by patients in the qualitative patient interview study and were included in the SOWS-Gossop. However, the SOWS-Gossop omits evaluation of several short-acting opioid withdrawal symptoms that are considered relevant and meaningful and described as some of the most severe acute withdrawal symptoms by patients (e.g., nausea, vomiting, diarrhea) as evidenced by the qualitative patient interviews.

Additionally, in the patient interview study, patients described experiencing dysphoria, anger, anxiety, and other emotional problems during acute opioid withdrawal and stated these symptoms may continue (perhaps in varying severity) beyond acute opioid withdrawal phase. While these concepts may not necessarily be confined to acute opioid withdrawal phase, patients considered them relevant and important in the target patient population.

Refer to the clinical review for relevant discussion on signs and symptoms of short-acting opioid withdrawal symptoms.

Interestingly, earlier versions of the SOWS-Gossop included questions related to gastrointestinal symptoms, which were later removed primarily based on quantitative evaluation (Gossop et al, 1990). This reviewer recommends evaluating both qualitative (e.g., patient input, experts input) and quantitative properties of an instrument when considering item reduction process during a COA development. Future iteration of the SOWS-Gossop should evaluate withdrawal symptoms more comprehensively using recommended approaches.

Furthermore, this reviewer has additional comments regarding the SOWS-Gossop as below:

- While the item “feeling sick” may be a broad and ambiguous concept, it is likely that this question may be capturing a global impression of symptoms experienced by patients as many patients during qualitative interviews described “feeling sick” as experiencing nausea, vomiting, diarrhea, flu-like symptoms among others. Sponsors should consider specificity when assessing relevant symptoms in the target patient population.*
- Regarding the “heart pounding” item, while this item was endorsed by 80% of participants but it was first identified in the 19th interview. Considering that certain important concepts were excluded from the questions, this item’s utility is questionable.*
- While 100% of participants were able to explain what yawning meant, yawning was only spontaneously reported by 2 (10%) of the participants. Clinical importance of this item is unclear, especially when compared to excluded concepts such as diarrhea, vomiting, and nausea.*
- Recall period instructions provided to patients appear confusing. For example, asking patients to rate their symptom severity “during baseline or since the last time [the patient] completed this test” may appear confusing to patients to validly recall requested*

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information. Such a major modification to recall period/instruction should be cognitively debriefed in patient interviews. Of note, the SOWS-Gossop was designed with a recall period of last 24 hours.

- *SOWS-Gossop patient instructions describe the PRO instrument as a “test,” which could be misinterpreted by patients as an exam and patients may respond to each item on the basis of desired condition rather than on their actual condition. Instead, terminology such as “questionnaire” may be used to describe the PRO instrument.*

Overall, this reviewer recommends modifications to the SOWS-Gossop instrument for use in future drug development programs intended to assess symptoms of opioid withdrawal that include a more comprehensive assessment of clinically relevant and meaningful symptoms in the target patient population. Because results obtained using a PRO instrument can vary according to the instructions given to patients, this reviewer recommends sponsors to use PRO instruction that is appropriate, clear, and easy to understand for patients to validly recall the information requested and complete the PRO instrument as it is intended. Sponsor should engage FDA review division early and throughout drug development to ensure the development and implementation of fit-for-purpose PRO instruments.

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant provided documentations of other measurement properties (psychometric properties) using pooled data across treatment groups from the two phase 3 clinical trials (USWM-LX1-3002; USWM-LX1-3003-1). This reviewer describes key elements of psychometric properties based on review of the SOWS-Gossop PRO Evidence Dossier. Refer to the SOWS-Gossop PRO Evidence Dossier for additional information.

At baseline, n=555 patients with complete instruments were included for the analyses from the clinical trials USWM-LX1-3002 and USWM-LX1-3003-1.

Reliability: Because clinical trials measure change over time, the adequacy of a PRO instrument for use in a clinical trial depends on its reliability or ability to yield consistent, reproducible estimates of treatment effect. Reliability of the SOWS-Gossop was assessed using internal consistency and test-retest methods.

- Internal consistency (defined as the extent to which items within a scale are related to each other) was calculated using Cronbach’s alpha. The Cronbach’s alphas for the SOWS-Gossop Total Score were assessed for baseline and days 1, 3, 5, and 7; the corresponding Cronbach’s alphas for each time points were 0.90, 0.90, 0.89, 0.87, and 0.86, respectively.

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- Test-retest reliability (defined as the stability or reproducibility of a PRO instrument over a short period of time during which the patient's status on the underlying concept has not changed) was evaluated between the SOWS-Gossop Total Score and the retest mean scores from baseline to day 1; days 4 to 5; and days 6 to 7, respectively. The intraclass correlation coefficients (ICC) were 0.78 (95% CI: 0.70-0.85) for baseline to day 1; 0.84 (0.79-0.89) for day 4 to day 5; and 0.88 (0.83-0.91) for day 6 to day 7, respectively.

Reviewer Comment: Reliability (internal consistency and test-retest) for the SOWS-Gossop instrument appears reasonable (recommended coefficients are >0.70).

Construct Validity: Construct validity is determined by evidence that relationships among items, domains, and concepts conform to a priori hypothesis concerning logical relationships that should exist with other measures or characteristics of patient population. The Applicant evaluated the SOWS-Gossop's convergent validity (defined as conceptually how similar or dissimilar concepts are more correlated), discriminant validity (defined as conceptually how similar or dissimilar concepts are less correlated), and known groups validity (defined as PRO instrument's ability to discriminate between clinically distinct patient groups) to support evidence of construct validity.

- Convergent Validity: Spearman correlation coefficients between the SOWS-Gossop and the OOWS-Handelsman, subject-reported Modified Clinical Global Impression (MCGI) of symptom severity, clinician-reported MCGI of symptom severity², Visual Analog Scale for Efficacy (VAS-E), and Clinical Opiate Withdrawal Scale (COWS) were calculated at baseline and days 1, 3, 5, and 7. Overall, the correlations were moderate to large and significant ($p < 0.0001$) for the SOWS-Gossop Total Score and the other instruments' scores at all timepoints ranging from 0.52 to 0.72 for the baseline assessment; 0.43 to 0.76 for day 1; 0.57 to 0.74 for day 3; 0.57 to 0.73 for day 5; and 0.43 to 0.68 for day 7. The applicant stated that given that most correlations with conceptually similar instruments were well over 0.4, there is good evidence for convergent validity of the SOWS-Gossop.

Refer to Appendix C for copies of MCGI.

- Discriminant Validity: Spearman rank correlation coefficients were calculated between the SOWS-Gossop and the subject-reported MCGI of side effects, and the clinician-reported MCGI of side effects. Correlations were generally small between the SOWS-Gossop Total Score and the other instruments' scores at all timepoints. Correlations ranged from -0.09 to -0.17 for the day 1 assessment; -0.01 to -0.13 for day 3; 0.05 to 0.14 for day 5; and 0.10 to 0.23 for day 7. Lack of consistent significance, low and partly negative correlations indicate that the SOWS-Gossop is measuring a different concept

² The Applicant incorrectly classified clinician-reported MCGI as an "observer-reported MCGI." Hereafter, "observer-reported MCGI" will be correctly referred to as clinician-reported MCGI throughout the review.

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than patient- or clinician- reported side effects and therefore these analyses support the discriminant validity of the SOWS- Gossop.

- **Known-Groups Validity:** Tests of known-groups validity were evaluated by examining differences in SOWS-Gossop Total Score by clinical severity groups using subject-reported and clinician-reported MCGI of symptom severity. The highest three response categories were combined for both the subject-reported and clinician-reported MCGI due to small sample sizes in each of these categories. There were five severity groups for the patient-reported MCGI: None (1) to Marked/Severe/Most severe (5,6,7) and five severity groups in the clinician-reported MCGI: Not ill (1) to Markedly/ Severely/ Most extremely ill (5,6,7). Overall F values for the ANOVA models used to test known groups validity controlling for age and gender were statistically significant ($p < 0.001$) at baseline, day 1, 3, 5, and 7 suggesting that the SOWS-Gossop Total Score is able to discriminate between MCGI severity groups.

Reviewer Comments: The construct validity evidence as assessed by convergent, discriminant and known groups validity generally appears supportive.

Ability to Detect Change: A review of ability to detect change (responsiveness/sensitivity) includes evidence that the instrument is equally sensitive to gains and losses in the measurement concept (i.e., symptoms) and to change at all points within the entire range expected for the target patient population. The responsiveness of the SOWS-Gossop was examined by estimating the mean change in SOWS-Gossop Total Score by change groups (worsening, no change, and improvement) on the patient- and clinician-reported MCGI symptom severity scale using ANCOVA for three time periods (Baseline to Day using 3002 data³; day 2 to day 4 and day 4 to day 5 using pooled data).

Note: The Applicant incorrectly classified clinician-reported MCGI as an “observer-reported MCGI.” “Observer-reported MCGI” should be correctly referred to as Clinician-reported MCGI.

The Tables 11a-c shows evidence to help support SOWS-Gossop’s ability to detect change (Source: SOWS-Gossop PRO Evidence Dossier, pp760-762).

³ The Applicant used data from trial 3002 only because MCGI was not assessed at baseline in study 3003-1.

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Table 11a. Responsiveness of SOWS-Gossop: ANCOVA with SOWS-Gossop Change Score from Baseline¹ to Day 1 by Changes in Patient- and Observer-reported MCGI Symptom Severity

	SOWS-Gossop Change Score			
	N; LS Mean (SE)	Overall F Test Value	P-value	Effect Size
Patient-reported MCGI of symptom severity (3 groups)		48.48	<0.0001	
Worsening (positive change)	69; 0.51 (0.51)			0.16
No change (0)	104; -1.32 (0.41)			0.19
Improvement (negative change)	70; -5.73 (0.51)			1.14
Observer-reported MCGI of symptom severity (3 groups)		31.59	<0.0001	
Worsening (positive change)	43; 0.41 (0.69)			0.20
No change (0)	127; -1.49 (0.40)			0.22
Improvement (negative change)	73; -4.54 (0.53)			0.90

¹ Data from trial 3002 only as MCGI not assessed at baseline in study 3003-1

Effect size is interpreted as small (0.20), moderate (0.50), or large (0.80)

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SE, standard error; SOWS, Subjective Opioid Withdrawal Scale

Table 11b. Responsiveness of SOWS-Gossop: ANCOVA with SOWS-Gossop Change Score from Days 2–4 by Changes in Patient- and Observer-reported MCGI Symptom Severity¹

	SOWS-Gossop Change Score				
	N	Mean (SE)	Overall F Test Value	P-value	Effect Size
Patient-reported MCGI of symptom severity (3 groups)			22.80	<0.0001	
Worsening (positive change)	25	1.44 (1.02)			0.19
No change (0)	74	-0.80 (0.59)			0.11
Improvement (negative change)	176	-5.33 (0.39)			0.79
Observer-reported MCGI of symptom severity (3 groups)			9.73	<0.0001	
Worsening (positive change)	15	0.49 (1.40)			0.06
No change (0)	86	-1.63 (0.59)			0.24
Improvement (negative change)	174	-4.76 (0.41)			0.70

¹ Pooled data from trial 3002 and 3003-1

Effect size is interpreted as small (0.20), moderate (0.50), or large (0.80)

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SE, standard error; SOWS, Subjective Opioid Withdrawal Scale

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Table 11c. Responsiveness of SOWS-Gossop: ANCOVA with SOWS-Gossop Change Score from Days 4–5 by Changes in Patient- and Observer-reported MCGI Symptom Severity¹

	SOWS-Gossop Change Score			Effect Size
	N; LS Mean (SE)	Overall F Test Value	P-value	
Patient-reported MCGI of symptom severity (3 groups)		19.13	<0.0001	
Worsening (positive change)	31 1.93 (0.61)			0.31
No change (0)	131 -0.81 (0.30)			0.16
Improvement (negative change)	83 -3.20 (0.37)			0.62
Observer-reported MCGI of symptom severity (3 groups)		11.49	<0.0001	
Worsening (positive change)	20 2.58 (0.79)			0.50
No change (0)	155 -1.16 (0.28)			0.21
Improvement (negative change)	70 -2.62 (0.42)			0.49

¹ Pooled data from trial 3002 and 3003-1

Effect size is interpreted as small (0.20), moderate (0.50), or large (0.80)

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SE, standard error; SOWS, Subjective Opioid Withdrawal Scale

***Reviewer Comments:** Evidence provided for SOWS-Gossop’s ability to detect change (responsiveness) generally appears supportive. This reviewer also examined individual item level data submitted in response to FDA Information Request (Appendix B), which suggested descriptive improvement observed at individual items over time. Certain items such as “feeling sick” and “feeling of coldness” moved with a greater magnitude descriptively while other items such as “heart pounding” moved very little as patients.*

7 INTERPRETATION OF SCORES

The Applicant used anchor-based methods, using the patient-reported anchor scale called MCGI of symptom severity for the periods between baseline to day 1, day 2 to 4, and day 4 to 5, for score interpretation for the SOWS-Gossop. The Applicant stated that a change score of approximately 2-4 points is likely a small but meaningful improvement on the SOWS-Gossop Total Score (range 0 to 30), which can be used to identify responders to treatment.

The Tables 12a-c below show results from anchor-based analyses for the SOWS-Gossop using the two phase 3 clinical trials data (USWM-LX1-3002; USWM-LX1-3003-1).

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Table 12a. Anchor-based Score Interpretation Assessment for Changes in SOWS-Gossop Total Score: Mean SOWS-Gossop Change Scores Among Those Reporting 1 Category Change and 2 Categories Change in Patient-reported MCGI Scale from Baseline¹ to Day 1

	N	Change in SOWS-Gossop Score Mean (SD)
Patient-reported MCGI of symptom severity		
Worsening (≥1 positive category change)	69	0.9 (4.67)
No change (0 category change)	104	-1.1 (3.79)
Small improvement (1 negative category change)	44	-4.6 (3.58)
Improvement (2 negative category change)	13	-6.9 (4.99)
Large improvement (>2 category change)	13	-11.8 (6.10)

¹ Data from trial 3002 only as MCGI not assessed at baseline in study 3003-1

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale

Table 12b. Anchor-based Score Interpretation Assessment for Changes in SOWS-Gossop Total Score: Mean SOWS-Gossop Change Scores Among Those Reporting 1 Category Change and 2 Categories Change in Patient-reported MCGI Scale from Days 2–4¹

	N	Change in SOWS-Gossop Score Mean (SD)
Patient-reported MCGI of symptom severity		
Worsening (≥1 positive category change)	25	1.4 (6.50)
No change (0 category change)	76	-0.8 (3.54)
Small improvement (1 negative category change)	101	-3.4 (3.38)
Improvement (2 negative category change)	46	-5.9 (3.81)
Large improvement (>2 category change)	31	-11.5 (8.58)

¹ Pooled data from trial 3002 and 3003-1

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale

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Table 12c. Anchor-based Score Interpretation Assessment for Changes in SOWS-Gossop Total Score: Mean SOWS-Gossop Change Scores Among Those Reporting 1 Category Change and 2 Categories Change in Patient-reported MCGI Scale from Days 4–5¹

	N	Change in SOWS-Gossop Score Mean (SD)
Patient-reported MCGI of symptom severity		
Worsening (≥1 positive category change)	31	1.9 (4.25)
No change (0 category change)	134	-0.8 (2.58)
Small improvement (1 negative category change)	60	-1.9 (3.05)
Improvement (2 negative category change)	14	-6.1 (4.37)
Large improvement (>2 category change)	10	-7.1 (4.31)

¹ Pooled data from trial 3002 and 3003-1

Abbreviations: ANCOVA, analysis of covariance; LS, least-squares; MCGI, Modified Clinical Global Impression Scale; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale

Reviewer Comments: *The Applicant used recommended anchor-based methods to derive specific threshold or range of thresholds that may be considered clinically meaningful. While the SOWS-Gossop total score ranges from 0 to 30, where higher score is indicative of severe symptoms, a 2-4 points change appears small but possibly meaningful to patients. This reviewer recommends additional input from Clinical to ensure this small change is clinically important in the target patient population.*

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Applicant did not perform any language translation. The SOWS-Gossop instruments were administered in English and study participants were required to speak and read English. The Applicant stated that cultural consideration was specifically given to the Hispanic population, which accounted for nearly a quarter of participants. However, the Applicant did not believe any modifications were needed as the item content were evaluated and found to be relevant and understandable to this ethnic group.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

10 REVIEW USER MANUAL

The Applicant stated that there is no developer-written user manual for the SOWS-Gossop.

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11 KEY REFERENCES FOR COA

Gossop M. The development of a Short Opiate Withdrawal Scale (SOWS). *Addict Behav.* 1990;15(5):487–490.

E. APPENDICES

Appendix A: Short Opiate Withdrawal Scale (SOWS-Gossop)

Appendix B: NDA 209229 SOWS-Gossop COA Information Request

Appendix C: MCGI Patient and Clinician Versions & Scoring Information

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Appendix A: Short Opiate Withdrawal Scale (SOWS-Gossop)

(Source: PRO Evidence Dossier, Page 37)



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Appendix B: NDA 209229 SOWS-Gossop COA Information Request (DARRTS Reference ID 4218924)

We request following information to facilitate the review of clinical outcome assessment data in Study 1 and Study 2. Please provide two separate files corresponding to each study.

Study 1 (USWM-LX1-3002):

1. Descriptive statistics (N, mean, standard deviation, median, minimum, maximum, and % missing) for each SOWS-Gossop item for Days 1 to 7 (including at the time of randomization/baseline) by treatment arm.
2. Procedures used to handle PRO missing data (item level missing data and total score missing data).
3. Completion rates for the SOWS-Gossop instrument by each time point for Days 1 to 7 for both treatment arms. Provide the definition for what constituted a “completed” questionnaire.
4. Baseline SOWS-Gossop item distributions by response categories (i.e., “None,” “Mild,” “Moderate,” and “Severe”), and floor and ceiling effects for each SOWS-Gossop item.
5. The following cumulative distribution function (CDF) and probability density function (PDF) curves (see graphic examples provided below) by treatment arms (i.e., lofexidine 3.2mg/day vs. placebo), including sample sizes and median scores for each curve in each figure’s legend.
 - a. CDFs and PDFs of SOWS-Gossop total score change from baseline to Day 3 by treatment arms.
 - b. CDFs and PDFs of SOWS-Gossop total score change from baseline to Day 5 by treatment arms.

Study 2 (USWM-LX1-3003-1):

1. Descriptive statistics (N, mean, standard deviation, median, minimum, maximum, and % missing) for each SOWS-Gossop item for Days 1 to 7 (including at the time of randomization/baseline) by treatment arm.
2. Procedures used to handle PRO missing data.
3. Completion rates for the SOWS-Gossop instrument by each time point for Days 1 to 7 for both treatment arms. Provide the definition for what constituted a “completed” questionnaire.
4. Baseline SOWS-Gossop item distributions by response categories (i.e., “None,” “Mild,” “Moderate,” and “Severe”), and floor and ceiling effects for each SOWS-Gossop item.
5. The following CDF and PDF curves (see graphic examples provided below) by treatment arms (i.e., lofexidine 2.4 mg/day vs. lofexidine 3.2 mg/day vs. placebo), including sample sizes and median scores for each curve in each figure’s legend.
 - a. CDFs and PDFs of SOWS-Gossop total score change from baseline to Day 3 by treatment arms.
 - b. CDFs and PDFs of SOWS-Gossop total score change from baseline to Day 5 by treatment arms.

Clinical Outcome Assessment Review

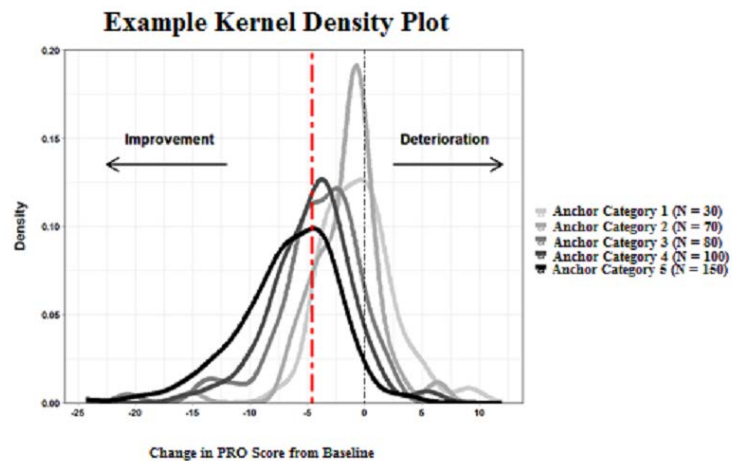
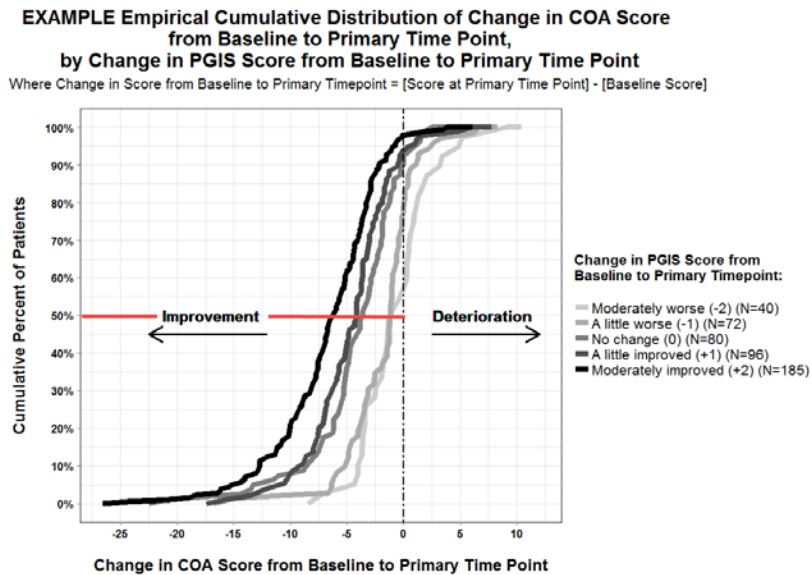
Nikunj Patel, PharmD

NDA 209229

Lofexidine

SOWS-Gossop (sx)

- c. CDFs and PDFs of SOWS-Gossop total score change from baseline to Day 7 by treatment arms.



Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 209229

Lofexidine

SOWS-Gossop (sx)

**Appendix C: Modified Clinical Global Impression – Patient and Clinician Versions
& Scoring Method**

MCGI – Patient Version

APPENDIX E: MCGI



(Source: PRO Evidence Dossier, Page 729)

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

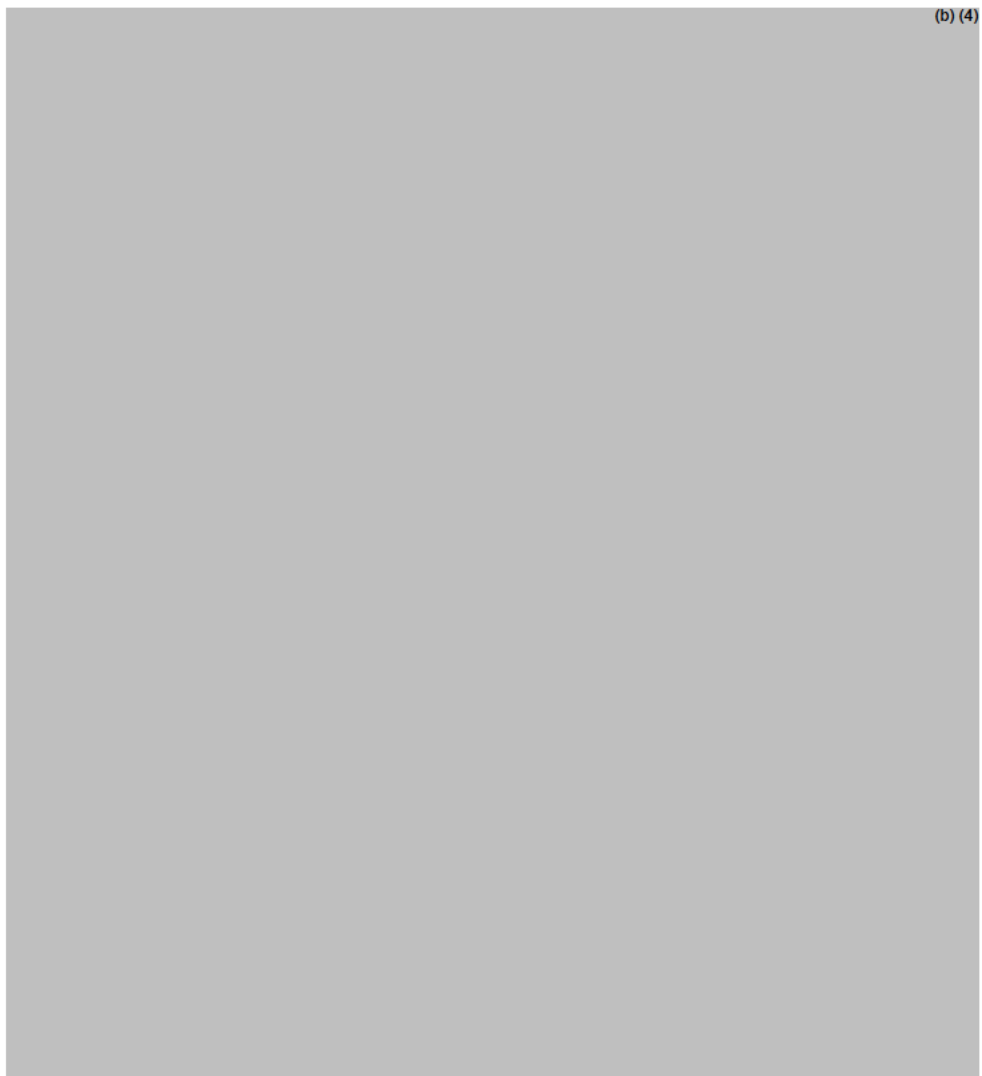
NDA 209229

Lofexidine

SOWS-Gossop (sx)

MCGI – Clinician Version

APPENDIX 3 Modified Clinical Global Impression (MCGI)



(Source: USWM-LX1-3003-1 Protocol, Page 84)

Clinical Outcome Assessment Review

Nikunj Patel, PharmD

NDA 209229

Lofexidine

SOWS-Gossop (sx)

Table 4. MCGI Scoring Method

MCGI	Score						
	1	2	3	4	5	6	7
Subject Scale							
Severity of Opiate Withdrawal Symptoms (a)	None	Between none and mild	Mild	Moderate	Marked	Severe	Most severe I ever had
Side Effects (b)	None	Slight, does not significantly interfere with daily activities	Moderate, significantly interferes with daily activities	Severe, greater than symptom relief			
Observer Scale							
Severity of Illness (a)	Not at all ill	Borderline ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Among the most extremely ill subjects
Side Effects (b)	None	Does not significantly interfere with subject's functioning	Significantly interferes with subject's functioning	Out-weighs therapeutic effect			

(a) Maximum score of 7.

(b) Maximum score of 4.

(Source: USWM-LX1-3003-1 Protocol, Page 56)

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/s/

NIKUNJ B PATEL

03/21/2018

ELEKTRA J PAPADOPOULOS

04/02/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Utilization Review

Date: February 19, 2017

Reviewer(s): Shekhar H. Mehta, PharmD MS
Drug Use Analyst
Division of Epidemiology II

Team Leader Rajdeep Gill, PharmD
Drug Use Analyst Team Leader
Division of Epidemiology II

Deputy Division Director LCDR Grace P. Chai, PharmD
Deputy Division Director for Drug Utilization
Division of Epidemiology II

Subject: Extent of Clonidine Use for Opioid Related Disorders

Drug Name(s): clonidine

Application Type/Number: multiple

Submission Number: multiple

Applicant/sponsor: multiple

OSE RCM #: 2017-2374

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EXECUTIVE SUMMARY

On March 27, 2018, a meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) will be held to discuss new drug application (NDA 209229; lofexidine hydrochloride), submitted by WorldMeds, LLC., with a proposed indication for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. If approved, lofexidine would be the first non-opioid (an alpha adrenergic-agonist) approved for this indication. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Epidemiology II (DEPI II) to provide drug utilization for clonidine and to evaluate possible use for management of acute opioid withdrawal. Clonidine is an alpha adrenergic-agonist and is currently available as oral immediate-release (IR) tablets and transdermal patches approved for the treatment of hypertension and oral extended-release (ER) tablets approved for the treatment of attention deficit hyperactivity disorder (ADHD). To provide informational context and background information, this review summarizes U.S. outpatient retail pharmacy utilization trends of clonidine from 2013-2017.

This review is particularly focused on oral clonidine (IR) tablets which accounted for 92% of total prescriptions dispensed compared to transdermal patches and extended-release tablets in 2017. An estimated 12.6 million prescriptions of oral clonidine IR tablets were dispensed and an estimated 2.7 million patients received clonidine IR tablets from U.S outpatient retail pharmacies in 2017. The majority of the outpatient retail prescriptions for clonidine IR tablets were written by general practitioners in 2017.

According to U.S. office-based physician survey data, clonidine IR tablets were primarily used to treat hypertension and an estimated 3% of total drug use mentions were reported to be associated with management of opioid related disorders (ICD-10, code F11).

1 INTRODUCTION

To provide informational context and background information for the Psychopharmacologic Drugs Advisory Committee (PDAC) meeting being convened to discuss new drug application (NDA 209229; lofexidine hydrochloride), this review summarizes U.S. outpatient retail pharmacy utilization trends of clonidine IR tablets from 2013-2017.

1.1 PRODUCT INFORMATION

Clonidine a centrally acting alpha-adrenergic agonist hypotensive agent available as tablets for oral administration intended to be used alone or concomitantly with other antihypertensive agents.¹ It is also available as a transdermal system providing continuous systemic delivery of clonidine for 7 days at an

¹ U.S. Food and Drug Administration: Drugs@FDA. clonidine IR tablets. Prescribing Information. Accessed January 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017407s0371bl.pdf

approximately constant rate². Clonidine ER is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications.³

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. See **Appendix 2** for detailed descriptions and limitations of the databases used to conduct these analyses. According to available prescription level data, over 92% of total clonidine dispensed from U.S. outpatient retail pharmacies was for clonidine IR tablets in 2017. Approximately 5% of U.S. outpatient retail prescriptions were for transdermal patches and 2 % for clonidine ER tablets. Therefore, we focused our analyses in this review clonidine IR tablet formulations.⁴

2.1 DATA SOURCES

The IQVIA, National Sales Perspectives™ (NSP) database was used to obtain the nationally estimated number of bottles of clonidine IR tablets sold from manufacturers to all U.S. channels of distribution to determine settings of care in 2017. The sales distribution data do not reflect what is being sold to or administered to patients directly; but these data do provide a national estimate of units sold from the manufacturers into the various channels of distribution.

The IQVIA, National Prescription Audit™ (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed for clonidine (stratified by formulation) from 2013-2017. In addition, the top prescriber specialties for clonidine IR tablets from U.S. outpatient retail pharmacies in 2017 were also obtained from this database.

The IQVIA, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients, stratified by patient age 0-1 years old, 1-12 years old, 13-17 years, 18-64 years, and 65 years and older who received a dispensed prescription for clonidine IR tablets from U.S. outpatient retail pharmacies, annually 2013-2017.

Syneos Health, TreatmentAnswers™ with Pain Panel, a U.S. office-based physician survey database, was used to obtain diagnoses associated with the use of clonidine IR tablets in 2017. Diagnoses data by number of drug use mentions⁵ were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence intervals were applied to the estimates. In addition, this database was used to obtain the most frequently reported drugs mentioned in association with the management of opioid related disorders (ICD-10 code F11) for 2017.

² U.S. Food and Drug Administration: Drugs@FDA. clonidine transdermal patches. Prescribing Information. Accessed January 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018891s028lbl.pdf

³ U.S. Food and Drug Administration: Drugs@FDA. clonidine IR tablets. Prescribing Information. Accessed January 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022331s013lbl.pdf

⁴ Source: IQVIA, National Prescription Audit (NPA). January 2017 – December 2017. Data Extracted February 2018. File: NPA 2017-2374 clon form 02-07-18.xlsx

⁵ A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

3 RESULTS

3.1 SETTINGS OF CARE

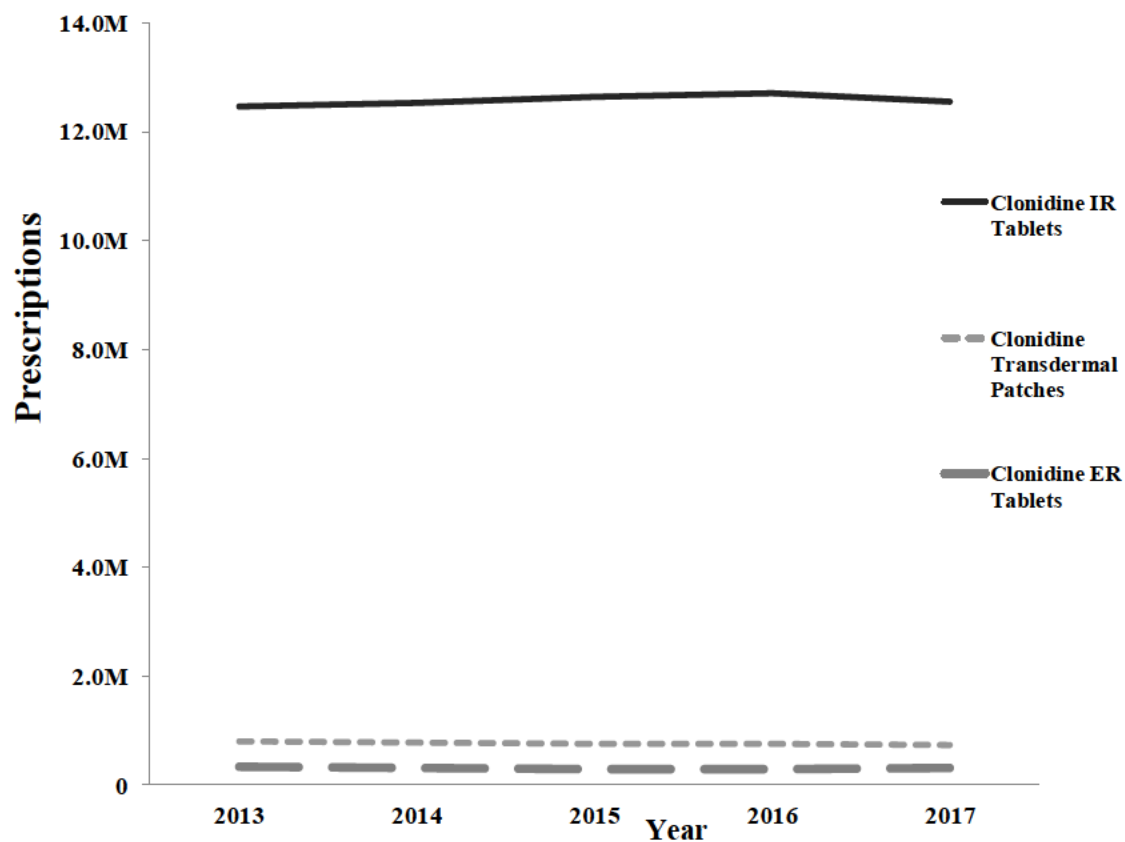
The IQVIA, National Sales Perspectives™ (NSP) database was used to determine the various settings of care where clonidine was distributed by the manufacturers. Sales data in 2017 showed that approximately 67% of clonidine IR tablets (bottles/packages) were sold to U.S. outpatient retail settings, 28% to non-retail pharmacies, and less than 5% to mail-order/specialty pharmacies. As a result, only outpatient retail pharmacy utilization patterns were examined, mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

3.2 PRESCRIPTION DATA

Figure 1 below and Table 6.1.1 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for clonidine stratified by formulation (IR and ER tablets, transdermal patches) from U.S. outpatient retail pharmacies, from 2013-2017, annually. Clonidine IR tablets accounted for more than 92%, transdermal patches accounted for 5% and ER tablets accounted for 2% of the total clonidine prescriptions dispensed during the study period. In general, the total number of prescription dispensed for clonidine IR tablets remained relatively consistent during the study period with an estimated 12.5 million prescriptions dispensed in 2017.

Figure 1

Nationally Estimated Number of Dispensed Prescriptions for Clonidine (IR Tablets, ER Tablets and Transdermal Patches) from U.S. Outpatient Retail Pharmacies, 2013-2017



Source: IQVIA, National Prescription Audit (NPA). 2013- 2017. Data extracted February 2018. File: NPA 2017-2374 clon form 02-07-18.xlsx

Table 6.1.2 in Appendix 1 provides the nationally estimated number of prescriptions dispensed for clonidine IR tablets from U.S. outpatient retail pharmacies stratified by the top prescribing specialties in 2017. An estimated 32% of total clonidine IR tablet prescriptions were written by general practitioners which include family practice, general practice, and internal medicine followed by nurse practitioners /physician assistants (21%) and psychiatrists (14%) in 2017.

3.3 PATIENT DATA

Table 6.1.3 in Appendix 1 provides the nationally estimated number of patients (stratified by patient age) who received a dispensed prescription of clonidine IR tablets, from U.S. outpatient retail pharmacies from 2013-2017, annually. The total number of patients who received dispensed prescriptions for clonidine IR tablets increased from an estimated 2.6 million patients in 2013 to 2.7 million patients in the 2017. Approximately 77% of patients who received dispensed prescriptions for clonidine IR tablets were 18 years or older.

3.4 DIAGNOSIS DATA

Table 2 below provides the diagnosis codes (ICD-10) in terms of drug use mentions associated with the utilization of clonidine IR tablets as reported by a U.S. office-based physician survey database during 2017. An estimated 1.5 million drug use mentions (63% of the total) were reported for ICD-10 “I10 essential (primary) hypertension”. An estimated 3% of the total drug use mentions (75,000 drug use mentions; 95% CI 24,000-127,000) were reported for ICD-10 code “F11 opioid related disorders” but this estimate falls below acceptable count to provide reliable estimates of national use. Upon exploring clonidine transdermal patches and ER tablets, there were no data recorded for diagnoses associated with management of opioid related disorders (ICD10, F11).⁶

Table 2

Nationally Estimated Number of Drug Use Mentions* for Clonidine IR Tablets (ICD-10), as Reported by U.S. Office-Based Physician Surveys, 2017

	Drug Use Mentions	Drug Use Mentions Share (%)	Drug Use Mentions 95% Confidence Interval
Grand Total	2,384,000	100%	2,096,000-2,673,000
I10 Essential (primary) hypertension	1,499,000	63%	1,270,000-1,727,000
G47 Sleep disorders	198,000	8.3%	115,000-281,000
I16 Hypertensive crisis	82,000	3.4%	28,000-135,000
F90 Attention-deficit hyperactivity disorders	79,000	3.3%	26,000-131,000
F11 Opioid related disorders	75,000	3.2%	24,000-127,000
I15 Secondary hypertension	61,000	2.6%	15,000-107,000
I12 Hypertensive chronic kidney disease	51,000	2.2%	9,000-94,000
R07 Pain in throat and chest	49,000	2.1%	8,000-90,000
F41 Other anxiety disorders	39,000	1.6%	2,000-75,000
I67 Other cerebrovascular diseases	30,000	1.3%	0-62,000
All Others	222,000	9.3%	134,000-311,000

Source: Syneos HealthTreatment Answers™ 2017. Data extracted February 2018. File: PDDA_2017-2374_clonidine_IR_Tabs_Dx3_02-06-18.xls

Note: The term "drug use mentions" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is

⁶ Source: Syneos HealthTreatment Answers™ 2017. Data extracted February 2018. Files: PDDA_2017-2374_clonidine_oral_IR_ER_patches_Dx3_02-07-18.xls and PDDA_clonidine_ER_ICD_10_chap_code_02-05-18.xls

mentioned. It is important to note that a "drug use mention" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Table 6.1.4 in Appendix 1 provides the most frequently reported drugs mentioned in association with the for management of opioid use disorders (ICD 10, Code F11) as reported by a U.S. office-based physician survey database for 2017. An estimated 5.2 million drug use mentions (90% of the total) were reported for buprenorphine and buprenorphine/naloxone combinations followed by naltrexone (3% of the total) and methadone (2.4% of the total). In addition to clonidine, other drugs such as lorazepam and gabapentin were also mentioned for the management of opioid related disorder but the estimates were below the threshold to provide reliable estimates of national use.

4 DISCUSSION

This review provides drug utilization data for clonidine IR tablets in the retail pharmacy settings and estimates the possible extent of use in the management of opioid related disorders. The data provided will serve as informational context and background information for the Psychopharmacologic Drugs Advisory Committee meeting being convened to discuss new drug application (NDA 209229) for another alpha adrenergic-agonist lofexidine hydrochloride.

Analysis of U.S outpatient retail prescription data for clonidine IR tablets showed that the number of prescriptions dispensed has remained relatively stable over the 5-year period from 2013 through 2017. An estimated 2.7 million patients received clonidine IR prescriptions in 2017 and majority of these patients being 18 years or older. Prescriptions for clonidine IR products were primarily written by family practice, general practice, and internal medicine specialties and an estimated 14% were written by psychiatrists. According to U.S. office-based physician survey data in 2017, reported drug use mentions of clonidine IR tablets were primarily associated with management of hypertension. Approximately 3% of total drug use mentions for clonidine IR were associated with opioid withdrawal symptoms. Based on these data, clonidine transdermal patches and ER tablets did not appear to be used for opioid withdrawal symptoms. Upon exploring for all the drug products that are used for management of opioid related disorders (ICD-10 Code F11), more than 95% of the drug use mentions were associated with products approved for this indication such as buprenorphine, buprenorphine/naloxone, naltrexone and methadone. Other drugs such as clonidine, lorazepam and gabapentin etc were also mentioned for management of opioid related disorders but these data were below the threshold to provide reliable estimates of national use. Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected mentions or occurrences may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 drug mentions do not represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that clonidine IR tablets were distributed primarily through outpatient retail pharmacy setting based on the IQVIA, National Sales Perspectives™ in 2017. As a result, we focused our analysis on the outpatient retail pharmacy settings; thus, these estimates may not apply to other settings of care in which clonidine is used (i.e., mail-order pharmacies, clinics, non-federal hospitals, etc.) In general, this survey database is best used to identify the typical uses for the products from an office-based physician setting and thus does not represent other settings where clonidine may be prescribed such as treatment clinics or hospitals. Therefore, use of clonidine in the management of opioid use disorders may be underestimated as the survey data presented are largely representative of office-based physicians and may

not represent prescribing patterns of care received from other settings such as specialty clinics, addiction centers, or hospitals.

5 CONCLUSION

This review provides the drug utilization patterns of clonidine IR tablets currently marketed in the U.S. and explored possible use for management of opioid related disorders. The outpatient retail pharmacy utilization of clonidine IR tablets appears to have remained relatively stable from 2013-2017. Although low, there is evidence of possible use of clonidine IR tablets for management of opioid related disorders according to U.S. office based physician survey data in 2017.

6 APPENDICIES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 6.1.1

Nationally Estimated Number of Dispensed Prescriptions for Clonidine (IR tablets, ER tablets and Transdermal Patches) from U.S. Outpatient Retail Pharmacies, 2013-2017

	2013		2014		2015		2016		2017	
	TRx (N)	Share(%)	TRx (N)	Share(%)	TRx (N)	Share(%)	TRx (N)	Share(%)	TRx (N)	Share(%)
Grand Total	13,579,933	100%	13,614,133	100%	13,697,408	100%	13,762,874	100%	13,590,823	100%
Clonidine IR Tablets	12,460,263	91.8%	12,540,447	92.1%	12,657,100	92.4%	12,720,724	92.4%	12,555,830	92.4%
Clonidine Transdermal Patches	793,095	5.8%	769,348	5.7%	745,743	5.4%	746,730	5.4%	736,449	5.4%
Clonidine ER Tablets	326,575	2.4%	304,338	2.2%	294,565	2.2%	295,420	2.2%	298,544	2.2%

Source: IQVIA, National Prescription Audit (NPA). 2012- 2017. Data extracted February 2018. File: NPA 2017-2374 clon form 02-07-18.xlsx

Table 6.1.2

Nationally Estimated Number of Dispensed Prescriptions for Clonidine IR Tablets from U.S. Outpatient Retail Pharmacies, by Provider Specialty, 2017

	Prescriptions(N)	Share(%)
Grand Total	12,555,830	100%
FP/GP/IM*	4,039,390	32.2%
NP/PA**	2,611,790	20.8%
Psychiatry	1,791,923	14.3%
Pediatrics	1,180,159	9.4%
Osteopathic Medicine	980,711	7.8%
Cardiology	534,843	4.3%
Nephrology	349,373	2.8%
All Other Specialties†	1,067,641	8.5%

Source: IQVIA, National Prescription Audit (NPA). 2017. Data Extracted February 2018.

File:NPA 2017-2374 clon rx special 02-05-18.xlsx

*FP/GP/IM: Family Practice, General Practice, Internal Medicine

**NP/PA: Nurse Practitioners, Physician Assistants

†All Other Specialties include all other medical specialties

Table 6.1.3

Nationally Estimated Number of Patients* who Received Dispensed Prescriptions for Clonidine IR Tablets* (Stratified by Patient Age) from U.S. Outpatient Retail Pharmacies, 2013-2017

	2013		2014		2015		2016		2017	
	Patients(N)	Share(%)	Patients(N)	Share(%)	Patients(N)	Share(%)	Patients(N)	Share(%)	Patients(N)	Share(%)
Grand Total	2,580,010	100%	2,589,850	100%	2,633,083	100%	2,665,503	100%	2,692,689	100%
0-17 Years Old	545,869	21%	573,755	22%	609,184	23%	614,183	23%	628,571	23%
0-1 Year	272	<1%	811	<1%	398	<1%	520	<1%	607	<1%
1-12 Years	373,861	68.5%	390,147	68.0%	410,893	67.4%	409,012	66.6%	412,858	65.7%
13-17 Years	178,036	32.6%	189,270	33.0%	204,752	33.6%	211,685	34.5%	222,260	35.4%
18 Years or Older	2,003,318	77.6%	2,005,940	77.5%	2,046,753	77.7%	2,066,080	77.5%	2,082,056	77.3%
18-64 Years	1,243,382	62.1%	1,274,823	63.6%	1,323,411	64.7%	1,335,505	64.6%	1,347,025	64.7%
65 Years or Older	769,754	38.4%	763,432	38.1%	763,369	37.3%	752,371	36.4%	747,625	35.9%
Unknown Age	138,596	5.4%	91,862	3.5%	28,932	1.1%	7,220	<1%	12,101	<1%

Source: IQVIA, Total Patient Tracker (TPT) Enhanced. 2013-2017, Extracted February 2018. File: TPT 2017-2374 clon IR tabs age 02-07-2018.xlsx

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

Table 6.1.4

Nationally Estimated Number of Drug Use Mentions* for Management of Opioid Related Disorders (ICD-10 Code F11), as Reported by U.S. Office-Based Physician Surveys, 2017

	Drug Use Mentions	Share(%) Drug Use Mentions	95% Confidence Interval Drug Use Mentions
Total Market	5,780,000	100%	31,000-6,229,000
Buprenorphine and Buprenorphine/Naloxone Combinations	5,182,000	89.7%	56,000-5,607,000
Naltrexone	173,000	3.0%	95,000-251,000
Methadone	140,000	2.4%	70,000-210,000
Clonidine	75,000	1.3%	24,000-127,000
Lorazepam	32,000	0.6%	0-65000
Gabapentin	23,000	0.4%	0-51000
Fluoxetine	21,000	0.4%	0-48000
Belladonna Alkaloids/Phenobarb	21,000	0.4%	0-48000
Loperamide	21,000	0.4%	0-48000
Naloxone	21,000	0.4%	0-47000
All Others	72,000	1.3%	22,000-122,000

Source: Syneos HealthTreatment Answers™ 2017. Data extracted February 2018. File: PDDA_2017-2374_Dx3_F11_molecuels_02-14-18.xlsx

Note: The term "drug use mentions" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use mention" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA, National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

IQVIA, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

SYNEOS Health, TreatmentAnswers™

SYNEOS Health, TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialist physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

SHEKHAR H MEHTA
04/02/2018

RAJDEEP K GILL
04/02/2018

GRACE CHAI
04/02/2018

Clinical Inspection Summary

Date	March 26, 2018
From	Damon Green, M.D., M.S., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Kim Compton, RPh, Regulatory Project Manager Pam Horn, M.D., Clinical Reviewer Celia Winchell, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	NDA 209229
Applicant	U.S. WorldMeds, LLC
Drug	Lucemyra (Lofexidine Hydrochloride)
NME	Yes
Therapeutic Classification/ Division Classification	Alpha-2-adrenergic receptor agonist/ Opioid Dependence
Proposed Indication	Mitigation of symptoms associated with opioid withdrawal: facilitation of completion of opioid discontinuation treatment.
Consultation Request Date	November 13, 2017
Summary Goal Date	March 19, 2018
Action Goal Date	May 16, 2018
PDUFA Date	May 26, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Riesenbergs, Molpus, Yadalam, and Roache were inspected in support of this NDA. The sponsor, U.S. WorldMeds, LLC., was also inspected. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final classification of the inspections of Drs. Riesenbergs, Molpus, and Yadalam was No Action Indicated (NAI). The preliminary classification of the inspection of Dr. Roache and the sponsor was NAI.

II. BACKGROUND

The purpose of this NDA was to assess the safety and efficacy of Lucemyra (Lofexidine) in mitigating symptoms associated with opioid withdrawal and facilitating the completion of opioid discontinuation treatment. The intention was to have a non-opioid medication suitable for treating signs and symptoms of opioid withdrawal with little to no abuse potential. Inspections were requested for the following protocols in support of this application:

Protocol USWM-LX1-3002: “A Phase III, Randomized, Multi-Center, Double-Blind, Placebo-Controlled Study of Safety and Efficacy of Lofexidine for Relief of Symptoms in Subjects Undergoing Inpatient Opioid Detoxification”

The study was conducted at 15 sites in the United States only beginning 06/16/2006 and ending on 10/26/2007. A total of 264 subjects were randomized.

The primary efficacy endpoint was the day 3 Short Opiate Withdrawal Scale (SOWS-Gossop) score and the time to dropout during the treatment phase.

Protocol USWM-LX1-3003-1: “A Phase 3, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1 to 7) Followed by Open-Label, Variable-Dose Lofexidine Treatment (Days 8 to 14)”

The study was conducted at 18 sites in the United States only beginning 06/17/2013 and ending on 12/24/2014. A total of 603 subjects were randomized.

The primary objective was to investigate the efficacy, safety, and dose-response of lofexidine (2.4 mg/day or 3.2 mg/day) in reducing withdrawal signs/symptoms and facilitating completion of withdrawal/extending treatment retention in subjects undergoing withdrawal from short-acting opioids in a double-blind inpatient setting (Days 1 to 7) followed by an open-label inpatient/outpatient setting (Days 8 to 14).

The primary efficacy endpoint was defined as the difference between the overall LS means from a pattern mixture model based on log-transformed SOWS-Gossop scores from Days 1 through 7.

Rationale for Site Selection

The inspections of Drs. Riesenbergs, Molpus, and Roache were requested due to high enrollment. Dr. Yadalam was noted to have a previous unrelated complaint which led to inspection (2011, classified VAI). The inspection of the sponsor was requested to assess, across sites, what quality measures were or were not in place to assure data integrity.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #1 Riesenberg, Robert 501 Fairburn Road, SW Atlanta, GA 30331	USWM-LX1-3003-1 Subjects: 69	09-19 Jan 2018	NAI
Site #2 Molpus, Robert 618 E. South Street, Suite 100 Orlando, FL 32801	USWM-LX1-3003-1 Subjects: 78	22-26 Jan 2018	NAI
Site #266 Yadalam, Kashinath 2770 3rd Ave, Suite 340 Lake Charles, LA 70601	USWM-LX1-3002 Subjects: 27	29 Jan 2018 to 01 Feb 2018	NAI
Site #245 Roache, John UTHSCSA - The Be Well Center Psychiatry – MC 7793, 7703 Floyd Curl Drive San Antonio, TX 78229	USWM-LX1-3002 Subjects: 40	20-27 Feb 2018	NAI*
Sponsor US WorldMeds, LLC 4441 Springdale Rd Louisville, KY 40241	USWM-LX1-3002 USWM-LX1-3003-1	19-23 Feb 2018	NAI*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations; Data unreliable.

*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Robert Riesenber

At this site, for Protocol USWM-LX1-3003-1, 81 subjects were screened and 69 subjects were enrolled. Of the enrolled subjects, 25 withdrew consent and 44 completed the study. None were lost to follow-up.

A total of 22 subject study records were reviewed in their entirety. Records reviewed included regulatory files, study protocol, subject medical history and research records, IRB approvals, subject eligibility criteria, informed consent procedures and documentation, source data and electronic case report forms, adverse event reporting, and study drug accountability.

The primary efficacy endpoint was verifiable, and there was no evidence of under-reporting of adverse events. No significant deficiencies were noted during this inspection.

2. Dr. Robert Molpus

At this site, for Protocol USWM-LX1-3003-1, 123 subjects were screened and 78 subjects were enrolled, and 28 subjects completed the study.

A total of 26 subject study records were reviewed. Records reviewed included informed consent forms, protocol amendments, signed investigator agreement, financial disclosure statement, IRB submissions and correspondence, adverse event reporting, clinical source data, electronic case report forms, concomitant medications, and sponsor monitoring activities.

The primary endpoint was verifiable, and there was no evidence of under-reporting of adverse events.

No Form FDA 483 was issued at the close of the inspection. However, discussion items included:

- Of the 15 subjects having dose hold deviations (a missed dose hold), one subject (b) (6) lofexidine 3.2mg) had a dose hold deviation, which the site did not report to the sponsor. However, the sponsor did report this as a protocol deviation.
- Six subjects (b) (6), placebo; (b) (6) lofexidine 2.4mg; (b) (6) lofexidine 3.2mg; (b) (6), lofexidine 3.2mg; (b) (6) lofexidine 3.2mg; (b) (6), placebo) had positive urine drug screens unreported as a deviation. Dr. Molpus reported them as “false positives.” The sponsor did report the six subjects as protocol deviations.
- Two subjects took concomitant medications during the inpatient portion of the study without receiving concurrence from the medical monitor. Although this was not recorded as a deviation, the medications were documented in the source log and eCRF correctly.
 - Subject (b) (6) lofexidine 3.2mg: Cipro
 - Subject (b) (6), placebo: Ventolin and Advair

Reviewer’s comment: As per the inspector, the site made corrections by the sponsor’s guidance throughout the study, re-trainings were done as necessary, and deviations were reported accurately.

3. Dr. Kashinath Yadalam

At this site, for Protocol USWM-LX1-3002, 36 subjects were screened and 27 subjects were enrolled. 20 subjects discontinued prior to the final study visit while 7 subjects completed the study.

Out of all the enrolled subjects, 16 subject study records were reviewed. Records reviewed include regulatory files, study protocol, subject medical history and research records, IRB approvals, subject eligibility criteria, informed consent procedures and documentation, source data and case report form evaluation, adverse event reporting, and study drug accountability, and monitoring correspondence files.

The primary efficacy endpoint was verifiable, and there was no evidence of under-reporting of adverse events. Corrective actions promised in response to the previous inspection (2011, VAI) were verified and found to address all prior concerns. No significant deficiencies were noted during this inspection.

4. Dr. John Roache

At this site, for Protocol USWM-LX1-3002, 76 subjects were screened and 40 subjects were enrolled. Out of the enrolled subjects, one withdrew due to an adverse event (QTC prolongation), 32 withdrew consent, and the remaining 7 subjects completed the study.

A total of 20 subject study records were reviewed. The primary efficacy endpoint was verifiable, and there was no evidence of under-reporting of adverse events. No significant deficiencies were noted during this inspection.

5. US WorldMeds, LLC

This sponsor provided oversight for Protocols USWM-LX1-3002 and USWM-LX1-3003-1. Records reviewed included monitoring records for sites involved in the stated protocols, monitoring records for sites that were closed due to deviations, contracts, financial disclosures, investigational product accountability, organizational review, monitoring of clinical investigator (CI), selection of monitors and CIs, contract research organizations, quality assurance, safety and adverse event reporting, data collection and handling, and electronic records.

There was no evidence of under-reporting of adverse events. Overall, the sponsor appears to have exercised adequate oversight of this study.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Winchell
DAAAP /Project Manager/ Compton
DAAAP/Medical Officer/Horn
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Kronstein
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAMON C GREEN
03/26/2018

PHILLIP D KRONSTEIN
03/26/2018

SUSAN D THOMPSON
03/26/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	209229
Brand Name	Lucemyra
Generic Name	Lofexidine
Sponsor	US Worldmeds (USWM)
Indication	Mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.
Dosage Form	Tablet
Drug Class	Selective α 2A-adrenergic receptor agonist
Therapeutic Dosing Regimen	3.2 mg/day (0.8 mg QID)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	2.0 mg as a single dose.
Submission Number and Date	SDN002 – 07/28/2017
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

Throughout the review, the total lofexidine dose was used rather than the free base dose.

1 EXECUTIVE SUMMARY

1.1 SUMMARY OF FINDINGS

QT prolongation and decrease in heart rate have been observed for lofexidine.

The mechanism of the observed QT prolongation is unknown. *In vitro* hERG data suggests that the observed QT prolongation is unlikely to be mediated via blockade of the hERG potassium channel. Overall, no large mean increase in the QTc interval has been observed in patients receiving lofexidine. This observation is supported by the presence of few QTc outliers (2 patients QTc $\geq$ 500 [1 in placebo], 9 patients with Δ QTc $\geq$ 60 [3 in placebo]) and few adverse events of interest per ICH E14. However, no dose or exposure-response relationship could be identified in the submitted studies for QTc prolongation.

There was an increase in the frequency of patients with bradycardia (<45 bpm) in the phase 3 trial (placebo: 3%; 2.4 mg: 7%; 3.2 mg: 20%). Bradycardia is a risk factor for torsade de pointes in the presence of QTc prolongation.

There was one case report of significant QTc prolongation (QTcF > 600 ms) when co-administered with methadone in an investigator-sponsored study, which was not included

in the ISS. In addition, there is a post-marketing case report of torsade de pointes for a subject receiving lofexidine and who had bradycardia (40 – 44 bpm).

1.2 SUMMARY OF THE SUBMISSION

The reviewer has assessed the QT data collected by the sponsor in healthy volunteers that showed QTcF prolongation and a decrease in heart rate and reached a similar conclusion as the sponsor. However, the profound decrease in heart rate (~20 bpm) impacts the ability to interpret the observed QTcF prolongation (section 5.1).

Analysis of the QTc data collected in patients on stable doses of buprenorphine does not suggest that lofexidine causes a large increase in the QTc interval when comparing buprenorphine + lofexidine to buprenorphine alone (section 5.5). However, an increase in the QTc interval was observed when comparing methadone + lofexidine to methadone alone (section 5.4). In addition, a DDI study with naltrexone was also conducted. In the naltrexone DDI study a single dose of 0.4 mg lofexidine was administered, and no difference between lofexidine alone compared to lofexidine + naltrexone was observed. However, as the study was conducted at a sub-therapeutic dose, the results cannot be extended to therapeutic dosing.

ECGs were also collected in patients with hepatic and renal impairment with a single lofexidine dose of 0.4 mg. The analysis of this data is limited to by-time analysis, due to the lack of an established concentration-QTc relationship for lofexidine. The hepatic and full renal impairment studies showed an increase in the maximum mean Δ QTc when comparing normal subjects to subjects with increasing degrees of organ impairment (sections 5.2 and 5.3). However, the number of subjects included in each of the studies per organ impairment group is too small to draw any definitive conclusions.

ECG data collected in phase 3 suggests that lofexidine does not cause large mean increases in the QTcF interval, with the maximum increase occurring on day 1 for both treatment arms (section 5.7). While the QTcF effect appears to be lesser when comparing day 7 to day 1, this observation cannot be used to conclude an absence of QTc prolongation over time.

Lastly, an integrated assessment of ECG outliers across all studies with ECG collection was also conducted and is presented in section 4.2. This analysis revealed few QTc outliers ≥ 500 or Δ QTc ≥ 60 ms, and, consistent with the results of other studies, an increase in the frequency of patients with bradycardia was also observed.

2 PROPOSED LABEL

Please note, that all labeling edits are suggestions only and we defer the final labeling to the review division. Please also note, that while we use total dose throughout our review that we are using free dose in our labeling recommendations to be consistent with other sections of the label.

Below are the proposed edits to the label proposed by the sponsor by section (gray heading). For each section we are including our proposed edits (addition, ~~deletion~~) and rational for our proposed edits are included to the right.

5.1 QT Prolongation	
<u>QT-IRT's proposed edits:</u> LOFEXIDINE (b) (4) prolongs the QT interval. (b) (4) (b) (4)	The information submitted from various study reports suggests that lofexidine prolongs the QTc interval, however, the extent is anticipated to be less than 20 ms. Thus, we are proposing to modify the W&P language to reflect this.
(b) (4) (b) (4) <u>Avoid LOFEXIDINE in patients with congenital long QT syndrome. ECG (b) (4) in patients with (b) (4) (b) (4) congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation (e.g. methadone) [see Adverse Reactions (6), Clinical Pharmacology (12.2)].</u>	(b) (4) the study suggests an increase and there is a case-report of significant QTc prolongation with methadone and lofexidine as well as the observed bradycardia with lofexidine, which is a risk factor for torsade de pointes in the presence of QTc prolongation.
7.2 Methadone	
<u>QT-IRT's proposed edits:</u> (b) (4) ECG monitoring is recommended in patients receiving methadone and lofexidine [see Warnings and Precautions (5.1)]. (b) (4) (b) (4)	Clarifying the need for ECG monitoring with concomitant use with methadone (see proposed edits to section 5.1).

12.2 Pharmacodynamics	
<u>QT-IRT's proposed edits:</u> <i>Cardiac Electrophysiology</i> (b) (4) single LOFEXIDINE doses of 1.44 to 1.8 mg produced maximum mean (b) (4) (b) (4) -change from baseline in QTcF (ΔQTcF) of 14.4 msec (upper two-sided 90% CI: 22.3 msec) and 13.6 msec (17.4 msec) for 1.44 and 1.8 mg respectively.	The proposal from the sponsor deviates from how QT data is presented within 12.2 and we are proposing edits to describe the study results by maximum-mean change (excluding the 4th time-point) using descriptive statistics consistent with Table 5 in the CSR. (b) (4) (b) (4)
In a Phase 3 placebo-controlled, dose-response study in opioid-dependent subjects, LOFEXIDINE was associated with a (b) (4) maximum mean prolongation of the ΔQTcF interval (b) (4) (b) (4) 7.3 (8.8) and 9.3 (10.9) msec at doses of 2.16 and 2.88 mg/day, respectively).	Because no positive control was included, it is not possible to conclude that the mean increase was (b) (4). Additionally, 90% CIs were added based on Table 3 in the Cardiac Safety Report.
(b) (4)	We do not agree with (b) (4) (b) (4)
<i>Patients with (b) (4) hepatic impairment</i> Administration of LOFEXIDINE to subjects with hepatic impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe hepatic impairment [see Use in Specific Populations (8.6)].	We propose removing (b) (4) from the title to be consistent with the text.

<u>Patients with renal impairment</u> <u>Administration of LOFEXIDINE to subjects with renal impairment was associated with prolongation of the QTc interval, which was more pronounced in subjects with severe renal impairment [see Use in Specific Populations (8.7)].</u>	We propose adding a similar subsection for renal as for hepatic impairment.
<u>LOFEXIDINE coadministered with methadone</u> (b) (4) LOFEXIDINE (2.88 mg/day) coadministered with methadone in 1618 methadone-maintained patients (80-120 mg/day) resulted in (b) (4) -a maximum mean increase from methadone alone baseline in QTcF of 9.1 (14.2) msec.	Because of concerns with the proposed exposure-response analysis (see next comment), we are proposing to include the descriptive statistics for the maximum mean ΔQTcF based on Table 24 in the CSR.
(b) (4)	We do not agree with (b) (4)
<u>LOFEXIDINE coadministered with buprenorphine</u> LOFEXIDINE ((b) (4) 2.88 mg/day) coadministered with buprenorphine in (b) (4) 21 buprenorphine-maintained patients (16-24 mg/day) resulted in a maximum mean increase in QTcF (b) (4) -of (b) (4) (5.6) msec compared to a buprenorphine alone baseline.	We do not agree with (b) (4) and therefore propose a similar representation of the

(b) (4)	results. The proposed numbers are extracted from Table 10 in the CSR.
	(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Lofexidine hydrochloride, 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1H-imidazole monohydrochloride, is a synthetic, non-narcotic, selective α 2A-adrenergic receptor agonist, the binding of which reduces release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity that occurs when the opioid is discontinued and its inhibitory effects on the system removed. Lofexidine is a structural analog to clonidine.

3.2 MARKET APPROVAL STATUS

Lofexidine has been marketed in the United Kingdom (UK) since 1992 by USWM's licensing partner, Britannia Pharmaceuticals, Ltd., as BritLofex™ Tablets 0.2 mg (lofexidine HCl) to relieve symptoms in patients undergoing opioid detoxification.

Reviewer's Comment: The BritLofex label includes cautionary language with regards to QT, such as avoid use in at risk patients or for patients receiving other QT prolonging medication.

3.3 PRECLINICAL INFORMATION

In USWM-LX0-PHA-0001, an assessment was conducted of the effect of lofexidine on the outward potassium current generated by human ether-a-go-go-related gene (hERG)-expressing Chinese hamster ovary (CHO) cells. At the highest concentration tested, density of the hERG currents was significantly decreased (16%) and could not be reversed during the 10-minute washout period. Based on these results, lofexidine appears to interact with the protein encoded by the hERG gene, and inhibit the IKr-like current at 53.44 µg/mL of lofexidine (free base). By comparison, mean peak plasma concentration of lofexidine at steady-state during 2.88 mg/day dosing with lofexidine is approximately 5 ng/mL (~20 nM, Table 1), a factor of 10,000 less. (Module 2.7.2 – Summary of Clinical Pharmacology Studies).

In a cardiovascular and respiratory safety study in dogs (USWM-LX0-PHA-0002), lofexidine at oral (capsule) doses of 0.3, 1, and 3 mg/kg had no adverse effects on blood pressure (systolic, diastolic, and mean arterial pressure), respiratory function (respiratory rate, blood oxygen saturation, and end tidal carbon dioxide), body weights, or mortality. There was a dose dependent occurrence of bradycardia. Animals also exhibited emesis, decreased body temperature, conduction disturbances, and prolongation of the QT interval at 3 mg/kg. Adverse effects were evident starting at 1-2 hours post dosing, and all were reversible.

The no-observed-adverse-effect level (NOAEL) was determined to be in the range of 0.3 to 1 mg/kg in this study (approximately 3-11 times the maximum therapeutic recommended human dose based on human equivalent dose [HED] calculations; see Table 2).

Reviewer's comments: Preclinical studies suggest that lofexidine has a low potential to inhibit hERG at clinical plasma concentration as was stated in a prior review as well (IND 47857, [02/19/2009](#)). The cardiovascular (CV) safety study in dogs revealed dose-dependent bradycardia (0.3, 1 and 3 mg/kg) and QT prolongation at the highest dose level (3 mg/kg).

3.4 PREVIOUS CLINICAL EXPERIENCE

The most frequently reported postmarketing AE with lofexidine has been hypotension. One death has been reported. The death was not considered related to lofexidine, but attributed to electrolyte imbalance secondary to dehydration resulting from vomiting and diarrhea during the subject's withdrawal from heroin. QT prolongation/torsades de pointes resulting in cardiac arrest was reported in a single subject. The subject recovered and the event was not attributed to lofexidine. Three cases of intentional overdose have been reported. Low pulse and blood pressure were reported in one case. Other than the single report of torsades de pointes, the AEs reported in the postmarketing environment are consistent with what has been observed in lofexidine clinical studies.

Additional information about the reported case of torsade is included below:

Patient (b) (6) was a 26-year-old male prisoner who received 0.2 mg lofexidine upon

arrival at the prison for opiate withdrawal. Prior to his arrival at the prison on (b) (6) he was cardiovascularly stable with a BP of 128/74 mmHg, a regular pulse of 68 bpm, and plasma potassium level of 4.9 mmol/l. Twenty minutes after receiving the lofexidine dose he reported feeling unwell, had repeated vomiting, a BP of 106/62 mmHg and bradycardia of 40-44 bpm. He was hospitalized, after which he collapsed and exhibited a long QT interval and torsades de pointes arrhythmia leading to cardiac arrest. The patient received cardiopulmonary resuscitation and cardioshock. Lofexidine therapy was discontinued and the patient completely recovered by (b) (6). The event was not attributed to lofexidine.

Reviewer's comments: The information provided for this case does not permit excluding the possibility of the adverse event being caused by lofexidine.

In addition, a case of QTc prolongation with lofexidine and methadone has also been reported, which has been previously discussed in a QT-IRT review (02/19/2009):

“A 44 year old white opiate dependent female enrolled in a protocol to assess the safety of taking daily Lofexidine with daily methadone. She had no known drug allergies, took no other drugs, and had never taken Lofexidine before.”

“An electrocardiogram before starting methadone showed sinus rhythm (70 beats/min) and QT/QTc 428/462 ms. After stabilization on methadone at 80 mg a day, an electrocardiogram still showed sinus rhythm (67 beats/min) and QT/QTc 428/449 ms (fig). She was then given Lofexidine with her daily dose of methadone, which was followed by brief hypotension (88/55 mm Hg) with mild drowsiness. Four hours after taking Lofexidine, an electrocardiogram showed sinus bradycardia (58 beats/min), QT/QTc 612/601 ms, and blood pressure 149/88 mm Hg (fig). The participant was otherwise asymptomatic. Within 24 hours, QT/QTc was 372/432 ms.”

Reviewer's comments: The IRT note in a previous review (02/19/2009) that in the case reported by Schmittner et al., 2004, the subject had a normal QT interval while on methadone, suggesting that the effect is related to either lofexidine or the combination of both drugs. The bradycardia reported in this case, which is probably related to lofexidine dosage, may contribute to the prolonged QTc effect described.

Since the case report of significant QTc prolongation after administration of lofexidine to patients on stable methadone raises the concern about the potential for an interaction between the two products. To explore this further, the sponsor has conducted a study of methadone + lofexidine (section 5.4). This study showed that lofexidine increases the QTc when co-administered with methadone as well as the decrease in heart rate observed in other lofexidine studies (section 5.4).

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of lofexidine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

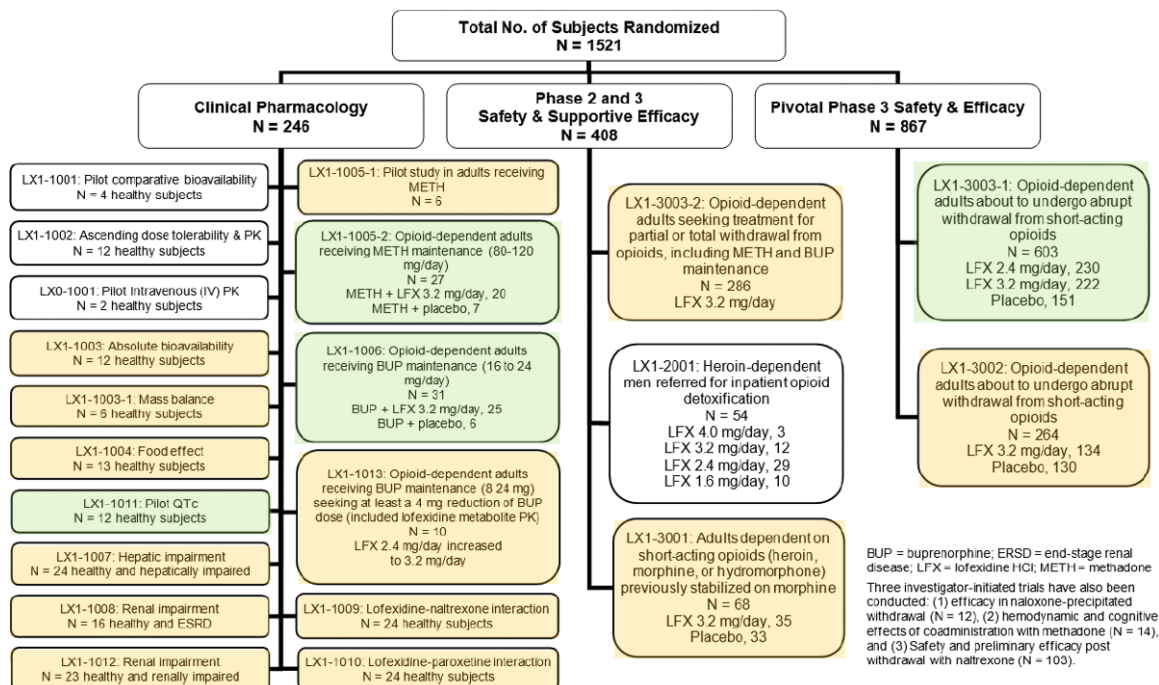
4.1 OVERVIEW

The sponsor previously requested a waiver because they considered lofexidine to be a QT prolonger with a similar magnitude to moxifloxacin. The sponsor also noted that it would not be possible to conduct a thorough QT study of lofexidine in healthy volunteers due to the observed bradycardia and hypotension and that conducting a thorough QT study in patients would not be feasible (DARRTs [06/25/2010](#); [10/12/2010](#)). The QT-IRT agreed with the sponsor. In addition, the QT-IRT review noted that as lofexidine is a QT prolonger that ECG monitoring should be included in future trials. The reviewer also recommended the sponsor to conduct a QT substudy within study 3003 (DARRTs [10/12/2010](#)).

The sponsor later submitted QT protocols for study 1005-1 (methadone + lofexidine; [02/15/2012](#)), 1005-2 (methadone + lofexidine; [07/09/2012](#)) and 1006-1 (buprenorphine + lofexidine; [03/28/2013](#)) as suggested by the agency ([06/23/2011](#)). The QT-IRT reviewed the protocols for studies 1005-1, 1005-2 and 1006, which did not result in identification of significant protocol issues.

The lofexidine development program consists of 21 studies (16 clinical pharmacology), 3 phase 2/3 studies and 2 phase 3 studies (Figure 1). In the figure studies are color-coded as follows: **Green**-coded studies correspond with studies with time-matched ECG and PK data that were reassessed in more detail in this review. **Green**- and **orange**-coded studies contain ECG measures and were included in the categorical outlier analysis table presented in section 4.2. Study LX1-1001 and phase 2 studies (LX1-2001) were not included in the integrated analysis because ECGs were collected on conventional machines and ECGs were not centrally read (see [sponsor's response to FDA IR 01-17-18](#) for details regarding studies included in the integrated outlier analysis).

Figure 1: Lofexidine clinical development program



Source: Colored version of Figure 1 in page 13 of the [Clinical Overview](#).

Appendix 6.2 includes tables with more details about the studies in Figure 1 and phase 2 study LX1-2003.

4.2 CATEGORICAL ECG OUTLIER ANALYSES

The sponsor submitted an integrated ECG outlier analysis for QTcF, PR, QRS and HR as [response to FDA IR 01-17-18](#). The integrated ECG outlier analysis includes all studies in the integrated summary of safety (ISS) except study LX1-1001 and phase 2 studies (LX1-2001 and LX1-2003). These three studies were not included because the ECGs were collected on conventional machines and ECGs were not centrally read (see [sponsor's response to FDA IR 01-17-18](#) for details regarding studies included in the integrated outlier analysis). Outlier analysis are available for these three studies in their corresponding clinical study reports. The integrated ECG outlier analysis tables below and in Appendix 6.2 list QTcF, PR, QRS and HR using the following cutoffs broken down by study, treatment and population:

- QTcF:
 - Absolute: ≥ 450 to < 480 ms, ≥ 480 to < 500 ms or ≥ 500 ms
 - Change from baseline: ≥ 30 to < 60 ms and ≥ 60 ms
- PR:
 - Absolute: ≥ 200 to < 220 ms and ≥ 220 ms
- QRS:
 - Absolute: ≥ 110 to < 120 ms and ≥ 120 ms
- HR:
 - Absolute: > 100 bpm and < 45 bpm, ≥ 45 to < 60 bpm

Table 1: Number and percentage (%) of subjects within QTcF interval ranges by absolute and change from baseline values (Safety Population).

Population	Study	Treatment	Subjects	QTcF range			Inc. from baseline	
				450<= <480 (ms)	480<= <500 (ms)	>=500 (ms)	30<= <60 (ms)	>=60 (ms)
Healthy Volunteers	LX1-1002	LFX	12	1 (8.3)	0	0	2 (16.7)	0
Healthy Volunteers	LX1-1003	LFX	12	2 (16.7)	0	0	3 (25.0)	1 (8.3)
Healthy Volunteers	LX1-1003-1	LFX	6	0	0	0	0	0
Healthy Volunteers	LX1-1004	LFX	13	0	0	0	1 (7.7)	0
Methadone maintained	LX1-1005-1	LFX	6	2 (33.3)	0	0	0	0
Methadone maintained	LX1-1005-2	LFX	19	7 (36.8)	1 (5.3)	0	1 (5.3)	0
Methadone maintained	LX1-1005-2	Placebo	7	1 (14.3)	0	0	0	0
Buprenorphine maintained	LX1-1006	LFX	24	2 (8.3)	0	0	0	0
Buprenorphine maintained	LX1-1006	Placebo	6	1 (16.7)	0	0	0	0
Hepatic impairment: Mild	LX1-1007	LFX	5	0	0	0	1 (20.0)	0
Hepatic impairment: Moderate	LX1-1007	LFX	6	1 (16.7)	1 (16.7)	0	1 (16.7)	0
Hepatic impairment: Normal	LX1-1007	LFX	6	1 (16.7)	0	0	0	0
Hepatic impairment: Severe	LX1-1007	LFX	6	3 (50.0)	2 (33.3)	0	1 (16.7)	0
Renal impairment: ESRD	LX1-1008	LFX	8	4 (50.0)	1 (12.5)	1 (12.5)	0	0
Renal impairment: Normal	LX1-1008	LFX	8	0	0	0	0	0
Healthy Volunteers	LX1-1009	LFX	24	3 (12.5)	0	0	1 (4.2)	0
Healthy Volunteers	LX1-1010	LFX	24	0	0	0	0	0
Healthy Volunteers	LX1-1011	LFX	12	2 (16.7)	0	0	7 (58.3)	0
Renal impairment: Mild	LX1-1012	LFX	6	2 (33.3)	0	0	0	0
Renal impairment: Moderate	LX1-1012	LFX	5	4 (80.0)	0	0	2 (40.0)	0
Renal impairment: Normal	LX1-1012	LFX	6	0	0	0	0	0
Renal impairment: Severe	LX1-1012	LFX	5	3 (60.0)	1 (20.0)	0	0	0
Buprenorphine maintained	LX1-1013	LFX	10	1 (10.0)	0	0	0	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	LFX 3.2	35	1 (2.9)	0	0	0	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	Placebo	33	1 (3.0)	0	0	0	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	LFX 3.2	134	12 (9.0)	1 (0.7)	0	24 (17.9)	3 (2.2)
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	Placebo	129	6 (4.7)	0	0	12 (9.3)	2 (1.6)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 2.4	252	15 (6.0)	1 (0.4)	0	43 (17.1)	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 3.2	251	18 (7.2)	2 (0.8)	0	45 (17.9)	2 (0.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	Placebo	163	3 (1.8)	1 (0.6)	1 (0.6)	9 (5.5)	1 (0.6)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX OL	148	0	0	0	2 (1.4)	0
Subjects undergoing withdrawal from various treatment scenarios	LX1-3003-2	LFX	286	16 (5.6)	0	0	31 (10.8)	0

Source: Table 1, pages 5-6 in sponsor's response to FDA IR 01-17-18 ([Link](#)).

Reviewer's comments: Table 1 shows there were only 2 subjects (one of them on placebo) with QTcF values greater than 500 ms within all the subjects in the safety population from 18 studies of lofexidine's development program. There were 11 subjects with $480\text{ ms} \leq \text{QTcF} < 500\text{ ms}$ in 6 of the 18 studies. Each of these 6 studies contributed with 1 or 2 subjects from some of their treatment groups, being one of the 11 subjects receiving placebo. In the larger Phase 3 studies (i.e., $N > 100$ subjects per treatment arm) the $480\text{ ms} \leq \text{QTcF} < 500\text{ ms}$ group represented $< 1\%$ of the subjects of their corresponding treatment group.

Table 2: Number and percentage (%) of subjects within HR interval ranges by absolute values (Safety Population).

Population	Study	Treatment	Subjects	HR < 45 (bpm)	45 ≤ HR < 60 (bpm)	HR ≥ 100 (bpm)
Healthy Volunteers	LX1-1002	LFX	12	0	10 (83.3)	0
Healthy Volunteers	LX1-1003	LFX	12	0	11 (91.7)	0
Healthy Volunteers	LX1-1003-1	LFX	6	2 (33.3)	4 (66.7)	0
Healthy Volunteers	LX1-1004	LFX	13	3 (23.1)	10 (76.9)	0
Methadone maintained	LX1-1005-1	LFX	6	4 (66.7)	2 (33.3)	0
Methadone maintained	LX1-1005-2	LFX	19	11 (57.9)	8 (42.1)	0
Methadone maintained	LX1-1005-2	Placebo	7	2 (28.6)	5 (71.4)	0
Buprenorphine maintained	LX1-1006	LFX	24	12 (50.0)	12 (50.0)	0
Buprenorphine maintained	LX1-1006	Placebo	6	0	5 (83.3)	0
Hepatic impairment: Mild	LX1-1007	LFX	5	1 (20.0)	3 (60.0)	0
Hepatic impairment: Moderate	LX1-1007	LFX	6	0	2 (33.3)	0
Hepatic impairment: Normal	LX1-1007	LFX	6	1 (16.7)	5 (83.3)	0
Hepatic impairment: Severe	LX1-1007	LFX	6	0	3 (50.0)	0
Renal impairment: ESRD	LX1-1008	LFX	8	0	2 (25.0)	0
Renal impairment: Normal	LX1-1008	LFX	8	1 (12.5)	4 (50.0)	0
Healthy Volunteers	LX1-1009	LFX	24	5 (20.8)	19 (79.2)	0
Healthy Volunteers	LX1-1010	LFX	24	5 (20.8)	19 (79.2)	0
Healthy Volunteers	LX1-1011	LFX	12	2 (16.7)	9 (75.0)	0
Renal impairment: Mild	LX1-1012	LFX	6	2 (33.3)	3 (50.0)	0
Renal impairment: Moderate	LX1-1012	LFX	5	2 (40.0)	3 (60.0)	0
Renal impairment: Normal	LX1-1012	LFX	6	0	5 (83.3)	0
Renal impairment: Severe	LX1-1012	LFX	5	0	3 (60.0)	0
Buprenorphine maintained	LX1-1013	LFX	10	3 (30.0)	6 (60.0)	1 (10.0)
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	LFX 3.2	35	2 (5.7)	11 (31.4)	1 (2.9)
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	Placebo	33	0	7 (21.2)	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	LFX 3.2	134	26 (19.4)	85 (63.4)	2 (1.5)
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	Placebo	129	2 (1.6)	37 (28.7)	6 (4.7)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 2.4	252	17 (6.7)	163 (64.7)	5 (2.0)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 3.2	251	50 (19.9)	146 (58.2)	2 (0.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	Placebo	163	4 (2.5)	32 (19.6)	22 (13.5)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX OL	148	1 (0.7)	33 (22.3)	34 (23.0)
Subjects undergoing withdrawal from various treatment scenarios	LX1-3003-2	LFX	286	28 (9.8)	162 (56.6)	4 (1.4)

Source: Table 4, pages 11-12 in sponsor's response to FDA IR 01-17-18 ([Link](#)).

Reviewer's Comment: Consistent with the results of the healthy volunteer study, bradycardia was observed across studies in the development program shown in Table 5. Additionally, the proportion of patients with heart rate <45 bpm was observed to be dose-dependent in study 3003-1 (placebo: 2.5%, lofexidine 2.4 mg: 6.7% and lofexidine 3.2 mg: 19.9%).

Appendix 6.3 includes categorical ECG outlier tables for PR and QRS, which showed no clinically significant differences in outliers between treatment groups.

5 REVIEWERS' ASSESSMENT

As noted previously, the sponsor requested a waiver for a TQT study because it is not possible to conduct a thorough QT study for lofexidine. This request was based in part on

clinical experience with lofexidine, including an open-label study in healthy volunteers and experience from the UK. The QT-IRT agreed to the waiver request and suggested inclusion a QT substudy in phase 3. The agency also requested two DDI studies with lofexidine (methadone and buprenorphine).

The reviewer's assessment of lofexidine is therefore focused on: 1) evaluation of the QT prolongation in healthy volunteers; 2) assessment of the potential for an interaction between lofexidine and methadone/buprenorphine; 3) evaluation of the QT in patients; and 4) assessment of adverse events of clinical importance per ICH E14 (narrow and broad Standardized MedDRA Queries [SMQ] for "Torsade de pointes/QT prolongation"). In addition, the results of the hepatic and renal impairment studies as well as the naltrexone DDI study were also reviewed (b) (4)

5.1 EVALUATION OF THE EFFECTS OF LOFEXIDINE ON THE QTc INTERVAL IN HEALTHY VOLUNTEERS (LX1-1011)

The sponsor has conducted one open-label study of multiple doses of lofexidine (1.6 and 2.0 mg) on the QTc interval (LX1-1011), see Table 8 for information about ECG/PK timing. Of note, this study was not designed to exclude small mean increases on the QTc interval as we have previously noted (DARRTS [10/12/2010](#)).

The reviewer performed an independent analysis using the PK and ECG data submitted by the sponsor. While the primary endpoint of this pilot QT study (LX1-1011) was defined using QTcI, not all studies in lofexidine's development program included QTcI. Additionally, the data used to support the estimation of the individual QT/RR relationship is not adequate to cover the on-treatment changes in heart rate (Figure 2). We are therefore using QTcF for our analysis of the data. The reviewer's analysis showed that lofexidine prolongs the QTcF interval (Figure 3), consistent with the sponsor's results with QTcI and QTcF.

Figure 2: Distributions of HR by treatment period

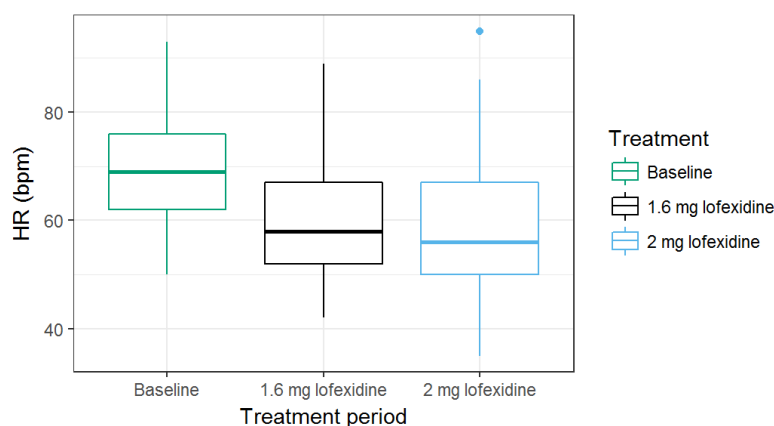
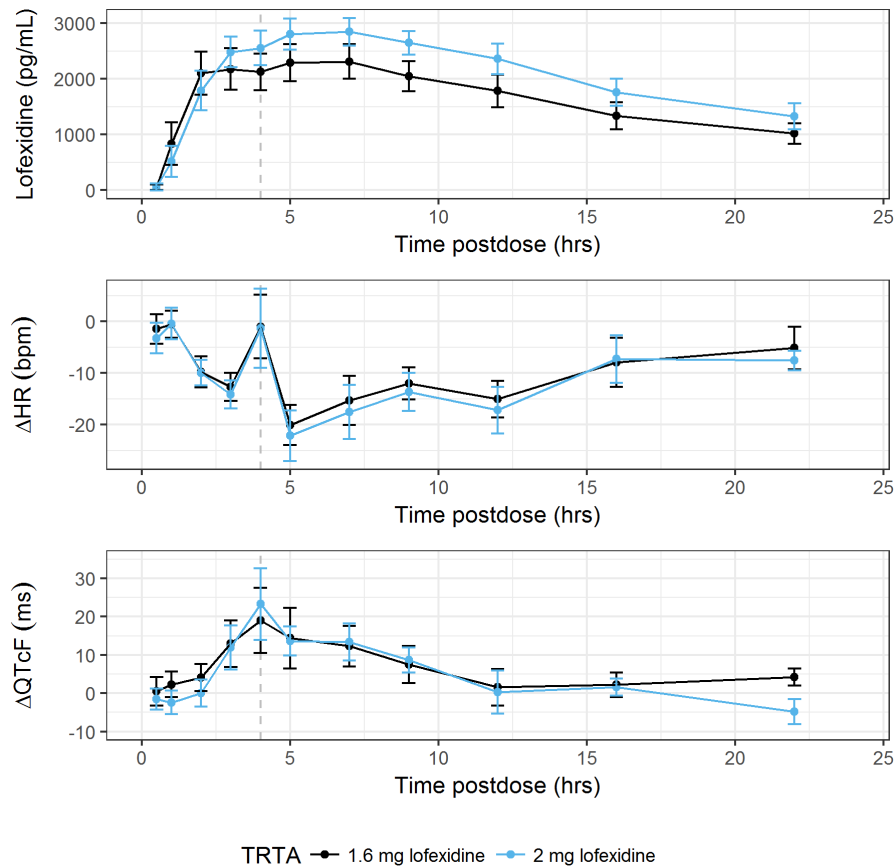
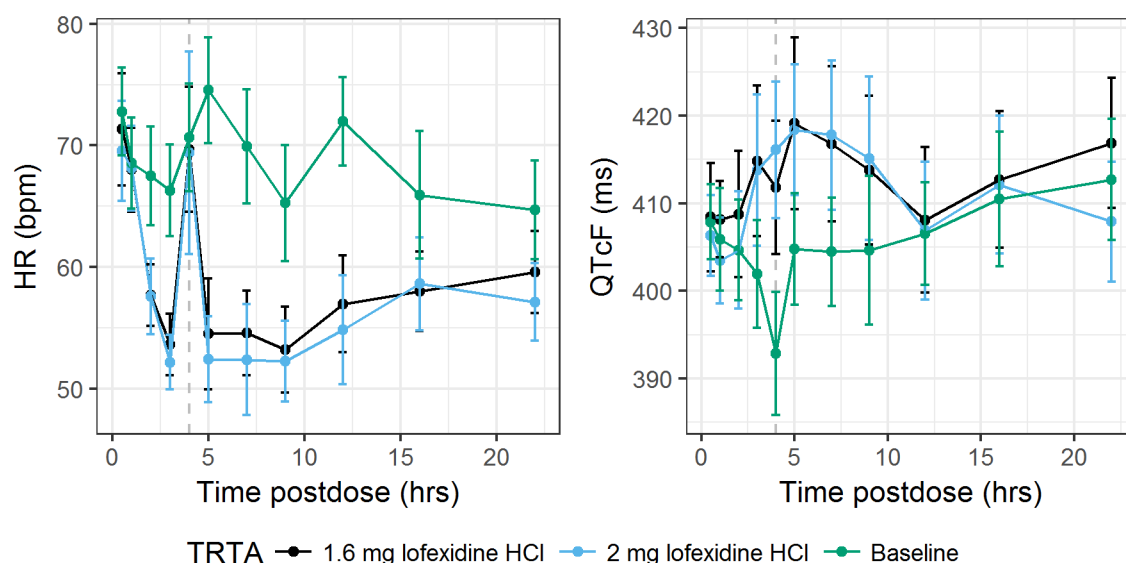


Figure 3: Study LX1-1011 lofexidine concentration and change from baseline in HR and QTcF per treatment arm and time-point. The dashed vertical line represents 4 hours postdose timepoint.



Of note, at 4 hours postdose, there was an increase in mean Δ QTcF prolongation greater than 10 ms and 20 ms in the 1.6 mg and 2 mg treatment arms, respectively (Figure 3). Similar abrupt changes in the time profiles of the mean QTcF and heart rate time-profiles (Figure 4). This was also noted by the sponsor and the study report includes the following conclusion regarding the peak Δ QTcF “*effect observed at 4 hours postdose was to a large extent driven by a pronounced shortening of the QTc interval seen at the 4-hour time point on baseline day*” ([ISS](#) page 4397). This peak also occurred before maximum lofexidine concentration was reached (4 hours vs. 5 to 6 hours postdose, Figure 3), and is likely a study artifact.

Figure 4: Study LX1-1011 HR and QTcF time-profiles per treatment arm



Lofexidine reduces heart rate and as was noted for QTcF above, there is an abrupt change at the 4 hours postdose timepoint in heart rate and the explanation for this observation is unclear. The sponsor suggests this increase in heart rate could be because “a light meal was served 30 minutes prior to dosing” (ISS page 4380) or “subjects having orthostatic vital signs taken at that time; only the 4 hour collection time for orthostatic vital signs coincided with an ECG extraction interval” (CSR page 40).

Lastly, mild PR prolongation was also observed in this study (mean change from baseline ~14 ms). However, no significant PR prolongation was observed across studies (Table 13).

5.2 EVALUATION OF THE HEPATIC IMPAIRMENT STUDY (LX1-1007)

Study LX1-1007 assessed the effects of hepatic impairment on the PK profile of lofexidine. A single dose of lofexidine HCl 0.4 mg was administered to 24 subjects, including 6 subjects with normal hepatic function and 6 subjects each with mild, moderate, and severe hepatic impairment. Subjects received lofexidine HCl as single oral doses of 0.4 mg, and ECGs were recorded via Holter monitoring with readings extracted in duplicate from recordings made under resting conditions before dosing and at 3, 4, and 8 hours postdose. ECGs were centrally evaluated.

This study included limited ECG collection (3, 4 and 8 h post-dose), which were collected in 24 subjects (6 normal) and 6 per hepatic impairment category. As the relationship between lofexidine concentration and Δ QTcF and Δ HR is unknown, this data was analyzed using a by-time analysis.

No trend for a decrease in Δ HR was observed by impairment group (Table 3), however, a trend of increase in Δ QTcF per hepatic impairment category was observed (Table 4). This increase in Δ QTcF does not appear to be explained by difference in C_{max} (normal: 0.8 ng/mL; severe hepatic impairment: 1.2 ng/mL).

Overall, the study showed a potential for greater QTc increase for patients with greater degree of impaired organ function. However, the number of subjects per organ impairment is too small to draw any definitive conclusions.

Table 3: Change in Δ HR after administration of a single dose of 0.4 mg by hepatic impairment group

Hours Post-dose	Normal Hepatic Function			Hepatic Impairment								
				Mild			Moderate			Severe		
	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
3	5	-7.0 (4.7)	-6.5 (-12.5, -1.5)	5	-2.9 (1.2)	-3.5 (-4.0, -1.0)	6	-5.4 (5.6)	-7.3 (-12.5, 2.5)	6	-7.1 (18.0)	-11.0 (-23.5, 27.0)
4	6	-6.7 (7.2)	-7.3 (-15.0, 4.5)	5	-1.8 (2.0)	-2.0 (-3.5, 1.5)	6	-8.0 (5.4)	-7.5 (-17.5, -3.0)	6	-8.3 (12.6)	-10.8 (-24.0, 11.5)
8	6	-4.0 (2.5)	-3.8 (-7.0, -1.5)	5	3.6 (3.2)	4.5 (-0.5, 6.5)	5	-5.5 (8.0)	-4.5 (-17.5, 4.5)	6	-7.0 (11.3)	-10.5 (-16.5, 14.5)

CI = confidence interval; max = maximum; min = minimum; SD = standard deviation.

Source: [ISS](#), Table 45, Page 85

Table 4: Change in Δ QTcF after administration of a single dose of 0.4 mg by hepatic impairment group

Hours Post-dose	Normal Hepatic Function			Hepatic Impairment								
				Mild			Moderate			Severe		
	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
3	5	-3.8 (7.1)	-7.0 (-10.0, 6.5)	5	5.2 (14.3)	4.5 (-9.5, 25.0)	6	13.5 (13.9)	13.3 (-4.5, 35.5)	6	16.4 (8.7)	13.8 (7.0, 32.0)
4	6	4.9 (10.2)	6.0 (-7.0, 17.0)	5	11.2 (15.8)	6.5 (-6.0, 30.0)	6	19.2 (14.0)	18.5 (5.0, 42.0)	6	21.1 (6.9)	19.3 (14.5, 33.5)
8	6	-7.0 (8.8)	-6.3 (-18.5, 5.5)	5	-5.2 (17.8)	-4.5 (-21.0, 23.)	5	13.1 (10.9)	8.0 (4.5, 31.0)	6	-0.3 (13.7)	0.5 (-24.5, 12.5)

CI = confidence interval; max = maximum; min = minimum; QTcF = heart rate-corrected QT interval (Fridericia's correction); SD = standard deviation.

Source: [ISS](#), Table 46, Page 85

5.3 EVALUATION OF THE RENAL IMPAIRMENT STUDIES (LX1-1008 AND LX1-1012)

Study LX1-1012 assessed the effects of a single dose of lofexidine 0.4 mg in 24 subjects, including 6 subjects with normal renal function and 6 subjects each with mild, moderate, and severe renal impairment. Subjects received lofexidine HCl as single oral doses of 0.4 mg, and ECGs were recorded via Holter monitoring with readings extracted from recordings made under resting conditions before dosing and at 3, 4, and 8 hours postdose. ECGs were centrally evaluated.

Limited ECG collection was included in the full renal impairment study (LX1-1012). For the analysis of the data from the renal impairment study, a by-time analysis was conducted as the relationship between lofexidine concentration and QTc is unknown.

The findings of the renal impairment study are similar to those of the hepatic impairment study in that the decrease in Δ HR was not consistent across renal impairment categories and an increase in Δ QTcF was observed that was greater in patients with greater renal impairment. The observed increase in Δ QTcF do not appear to be explained by differences in $C_{\max}$ (normal: 0.7 ng/mL; severe: 1.1 ng/mL). Of note, no difference between the Δ QTcF was observed in the reduced renal impairment study and no differences in $C_{\max}$ were observed between the end stage renal disease (ESRD) and normal renal function.

Overall, the study showed a potential for greater QTc increase for patients with greater degree of impaired organ function. However, the number of subjects per organ impairment is too small to draw any definitive conclusions.

Table 5: Change in Δ HR after administration of a single dose of 0.4 mg by renal impairment group

Hours Postdose	Statistics	Normal Renal Function	Renal Impairment		
			Mild	Moderate	Severe
3	N	5	6	6	5
	LS mean	-6.5	-10.3	-10.3	-5.3
	Standard error	2.36	2.17	2.16	2.43
	90% CI	(-10.7, -2.4)	(-14.1, -6.6)	(-14, -6.5)	(-9.6, -1.1)
4	N	5	6	6	5
	LS mean	-7.3	-11.3	-11.8	-6.7
	Standard error	2.11	1.94	1.92	2.18
	90% CI	(-11, -3.7)	(-14.7, -8)	(-15.1, -8.4)	(-10.5, -3)
8	N	5	6	6	5
	LS mean	-4.9	-10.3	-11.1	-4.5
	Standard error	2.44	2.24	2.22	2.50
	90% CI	(-9.2, -0.7)	(-14.2, -6.4)	(-15, -7.2)	(-8.9, -0.2)

CI = confidence interval; LS = least squares.

Source: [ISS](#), Table 51, Page 90

Table 6: Change in Δ QTcF after administration of a single dose of 0.4 mg by renal impairment group

Hours Postdose	Statistics	Normal Renal Function	Renal Impairment		
			Mild	Moderate	Severe
3	N	5	6	6	5
	LS mean	0.6	3.9	12.8	17.1
	Standard error	5.89	5.33	5.31	5.94
	90% CI	(-9.7, 10.8)	(-5.4, 13.1)	(3.6, 22.1)	(6.7, 27.4)
4	N	5	6	6	5
	LS mean	5.4	6.7	18.0	21.3
	Standard error	6.22	5.64	5.61	6.27
	90% CI	(-5.5, 16.2)	(-3.1, 16.5)	(8.2, 27.7)	(10.4, 32.1)
8	N	5	6	6	5
	LS mean	-6.6	1.0	12.1	13.7
	Standard error	4.40	3.95	3.92	4.46
	90% CI	(-14.3, 1)	(-5.9, 7.9)	(5.3, 19)	(5.9, 21.4)

CI = confidence interval; LS = least squares; QTcF = heart rate-corrected QT interval (Fridericia's correction).

Source: [ISS](#), Table 52, Page 91

5.4 ASSESSMENT OF THE EFFECTS OF LOFEXIDINE ON METHADONE INDUCED QTc PROLONGATION (STUDY LX1-1005-2)

Study LX1-1005-2, was a randomized, double-blind, placebo-controlled, multiple ascending-dose study of lofexidine HCl in 26 subjects. The primary objective of the study was to assess QTc interaction effects between lofexidine and methadone. Subjects were randomized in a 3:1 ratio to receive up to 4 tablets of lofexidine HCl (0.2 mg/tablet) QID or 4 tablets of placebo QID.

In this study 6 subjects completed the placebo treatment and 16 subjects could be titrated to the targeted lofexidine dose (3.2 mg), which are labeled as group A. The analysis described below only includes subjects in group A using data from days 0 and 5.

The reviewer performed an independent analysis using the PK and ECG data submitted by the sponsor. Figure 5 shows the time-profiles for the pharmacokinetics of methadone + lofexidine (A-Active) and methadone + lofexidine (A-Placebo) for the initial methadone alone day (Day 0, solid lines) and lofexidine plateau day (Day 5, dashed lines). No clinically significant PK interaction between methadone and lofexidine was observed, however, a slight increase in methadone PK was observed after co-administration with lofexidine.

Figure 5: Pharmacokinetic time profiles of lofexidine and methadone from the methadone + lofexidine arm (A-ACTIVE top panels) and methadone + placebo (A-placebo bottom panels) for study day 0 (solid lines) and lofexidine plateau day (day 5, dashed lines).

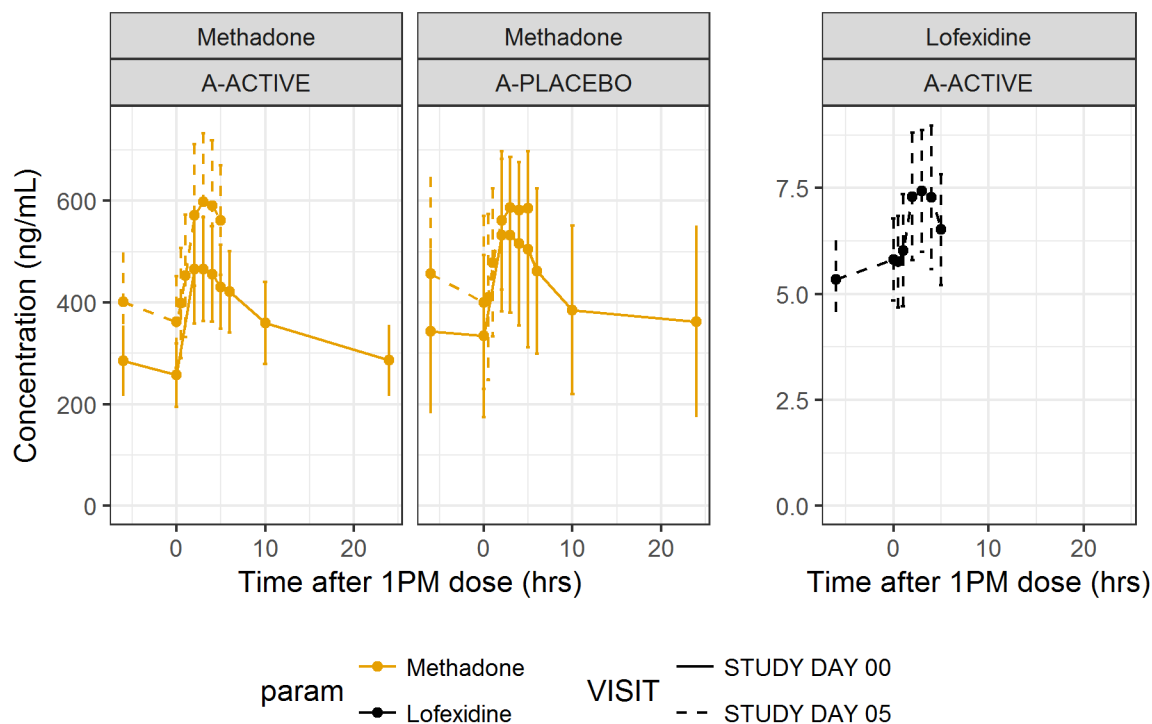
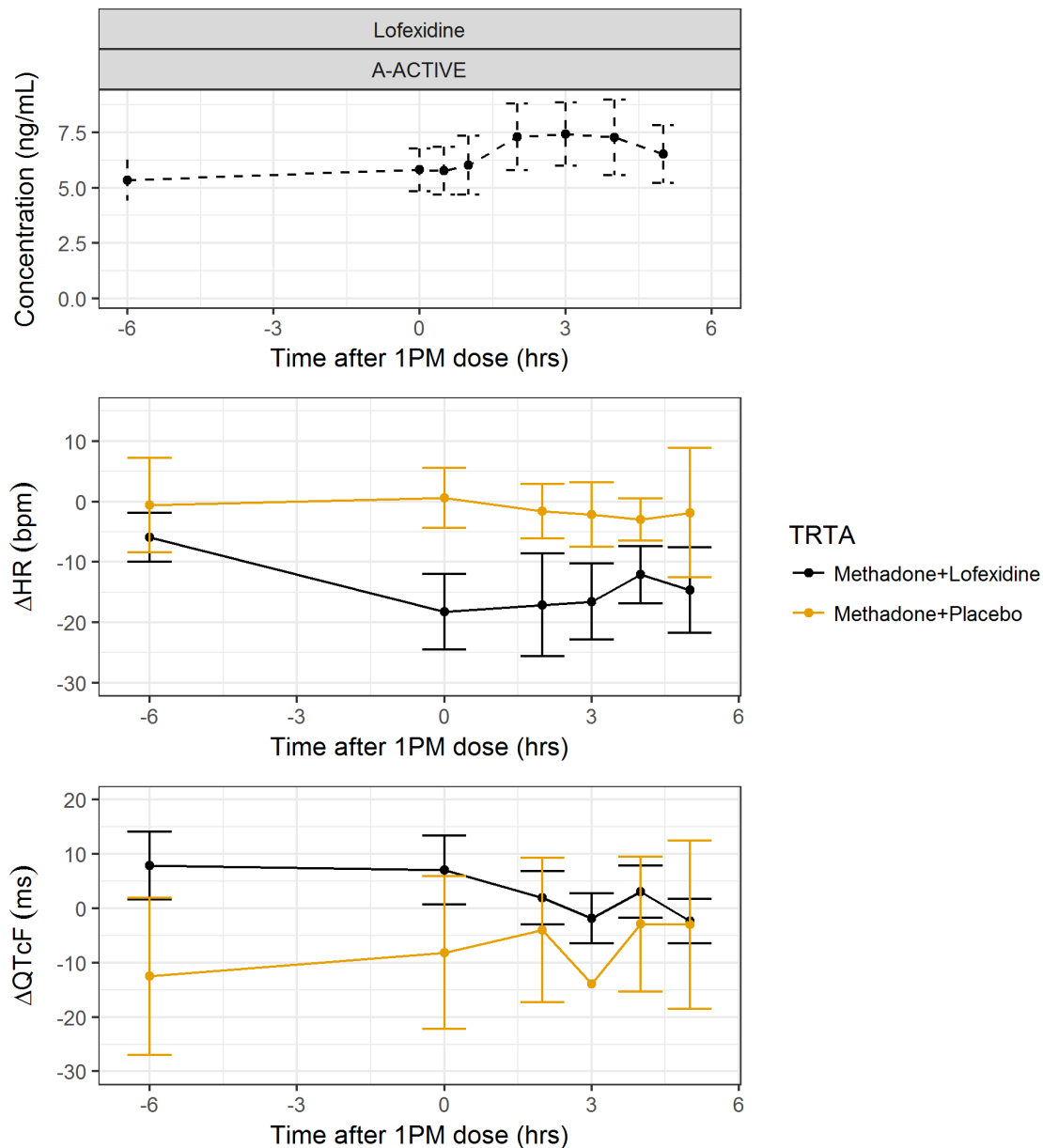


Figure 6 shows time-profiles for change from time-matched methadone alone steady state (day 0) for HR (Δ HR) and QTcF (Δ QTcF) per treatment arm on lofexidine plateau day

(day 5). Overall, the results of the by-time analysis by the reviewer were consistent with the sponsor's results. A decrease in heart rate was observed for methadone + lofexidine compared to the methadone alone day and an increase in mean Δ QTcF of 7.9 ms was observed. A slight increase in methadone PK was observed when co-administered with lofexidine. However, this slight increase is insufficient to explain the QTcF increase observed when methadone is co-administered with lofexidine.

Figure 6: Time profiles for lofexidine concentration on lofexidine plateau day (Day5) and change from time-matched methadone alone steady state (Day 0) for HR (Δ HR) and QTcF (Δ QTcF) per treatment arm (i.e., Δ = Day 5 – Day 0).



To evaluate the effects of lofexidine and methadone on the QTc interval, the sponsor conducted an exposure-response analysis. This analysis initially included methadone, lofexidine and an interaction between log-methadone and log-lofexidine concentrations with change from baseline (methadone alone) as the dependent variable. Because the interaction term was not statistically significant, it was dropped from the model. After dropping the interaction term, the sponsor conducted a univariate analysis, which was used to estimate the effects on the QTc interval for lofexidine.

To assess the appropriateness of this approach, the reviewer evaluated the time-course of lofexidine PK compared to changes in Δ QTcF and Δ HR, which is shown in Figure 6. This analysis showed changes in the Δ QTcF on lofexidine plateau day (day 5), which do not appear to be mediated by changes in the lofexidine plasma concentration, suggesting that a direct-response model as used by the sponsor is not appropriate. The lack of a direct effect is also consistent with the findings of the *in vitro* assay that suggests that the observed QTc prolongation for lofexidine is not mediated via blockade of the hERG potassium channel (section 3.3).

The sponsor also assessed the relationship between Δ QTcF (change from methadone alone) and methadone concentration, which did not reveal the presence of a relationship. However, as the baseline in the study was time-matched from steady state methadone-alone day, one would not have expected a relationship. To assess the relationship between methadone and QTcF, the reviewer used the methadone alone data and modeled the relationship between QTcF (dependent variable) and methadone concentration, with a random effect on intercept and slope. This analysis showed a slope of 16.6 ms per 1,000 ng/mL of methadone, which is in the range of the slope of 17 [90% confidence interval 12 to 22] ms per 1,000 ng/mL previously reported by Florian et al ([Florian et al Clin Pharmacol Ther 2012](#)).

Overall, the study suggests that lofexidine might increase the QTc interval compared to a methadone-alone baseline and based on a by-time analysis the maximum mean Δ QTcF was observed to be 7.9 ms. Additionally, a difference 20.4 ms was observed compared to lofexidine-placebo, however, this was a secondary analysis and only a small number of subjects received lofexidine-placebo (n=7). In addition, a decrease in heart rate was observed in the lofexidine arm (maximum mean Δ HR was -18 bpm), but not in the placebo arm.

5.5 ASSESSMENT OF THE EFFECTS OF LOFEXIDINE ON QTc WHEN COADMINISTERED WITH BUPRENORPHINE AT 100% MAINTENANCE LEVEL (STUDY LX1-1006)

Study LX1-1006 followed the same design as Study LX1-1005-2 and was a randomized, double-blind, placebo-controlled, multiple ascending-dose study of lofexidine in 30 subjects receiving buprenorphine maintenance for opioid dependence. The primary objective of the study was to assess lofexidine-related effects on QT/QTc in subjects receiving buprenorphine maintenance. Subjects were randomized in a 4:1 ratio to receive up to 4 tablets of lofexidine HCl (0.2 mg/tablet) QID or 4 tablets of placebo QID.

In this study 6 subjects were assigned to placebo and 21 subjects could be titrated to the targeted lofexidine dose (3.2 mg). The analysis described below only includes these 27 subjects labeled as group A.

The reviewer performed an independent analysis using the PK and ECG data submitted by the sponsor. Figure 7 shows the PK profile for buprenorphine alone day (Day 0, solid lines) vs buprenorphine + lofexidine (A-Active) or buprenorphine + placebo (A-Placebo) on the second plateau day (Day 5, dashed lines). No significant PK interaction was observed for lofexidine, buprenorphine or nor-buprenorphine.

Figure 7: Pharmacokinetic time profiles of buprenorphine, norbuprenorphine and from the buprenorphine+lofexidine arm (A-ACTIVE left panels) and buprenorphine+placebo (A-placebo right panels) for study Day 0 (solid lines) and lofexidine plateau day (Day 5, dashed lines).

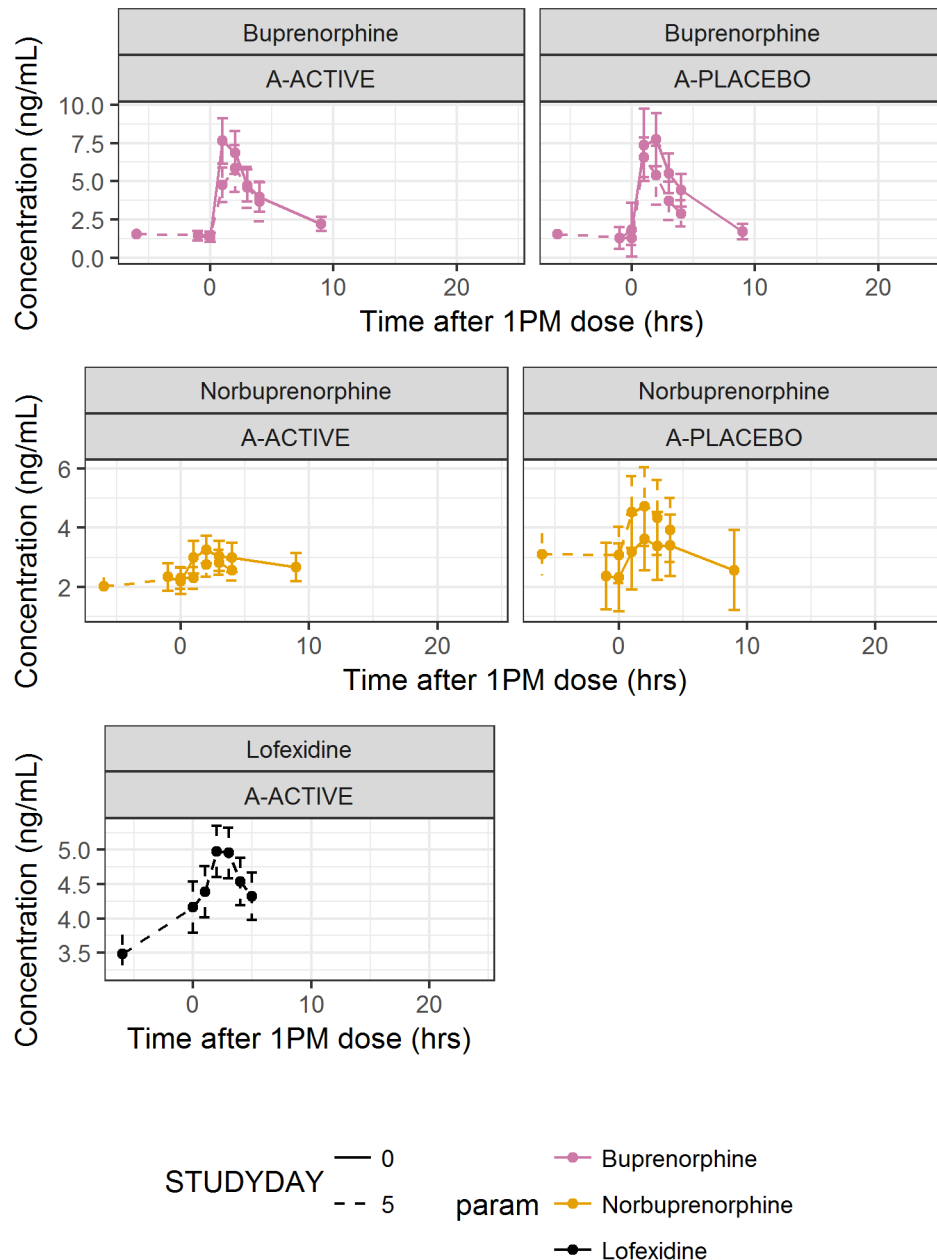
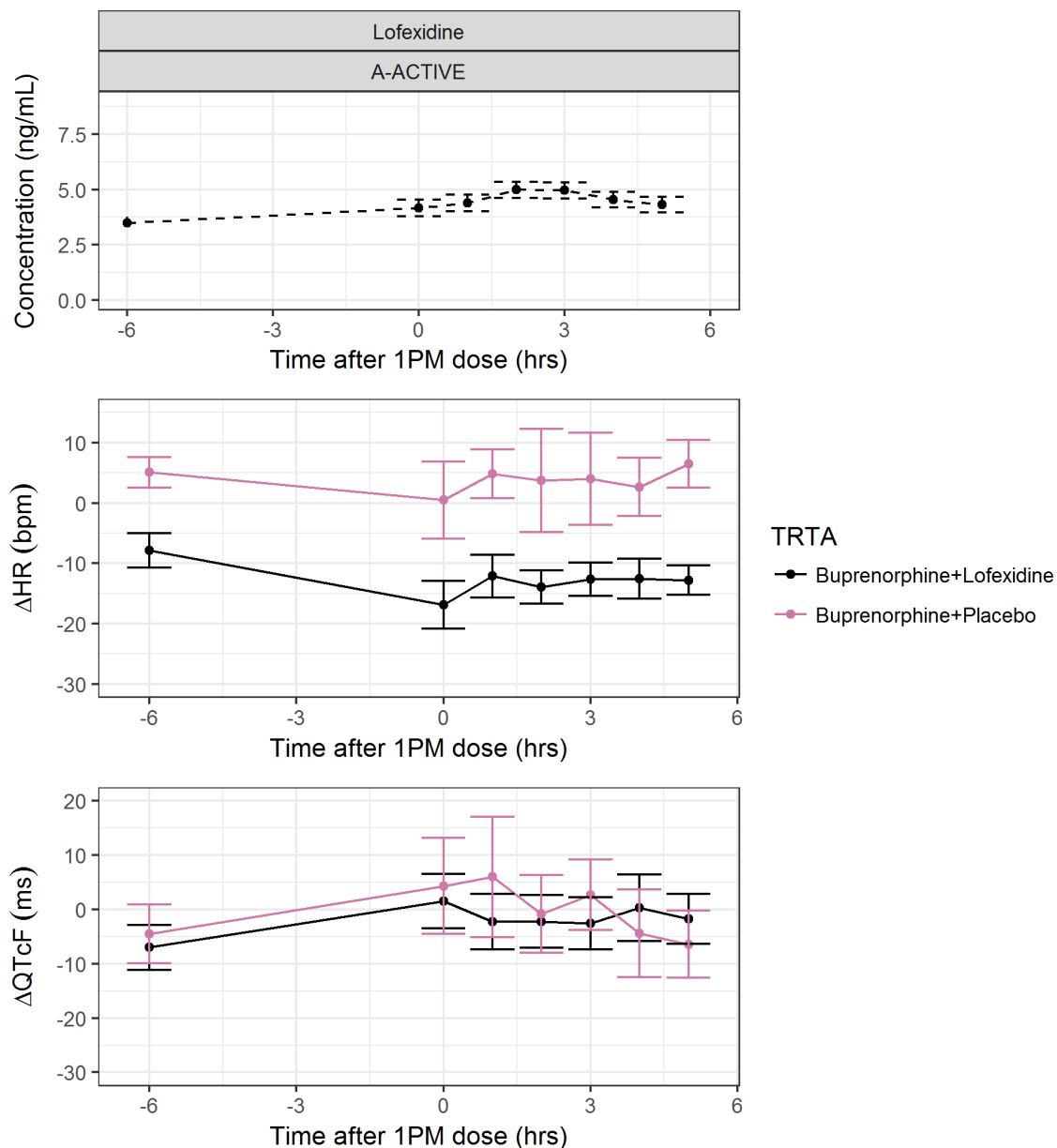


Figure 8: Time profiles for lofexidine concentration on lofexidine plateau day (Day5) and change from time-matched buprenorphine alone steady state (Day 0) for HR (Δ HR) and QTcF (Δ QTcF) per treatment arm (i.e., Δ = Day 5 – Day 0).



The sponsor carried out an exposure-response analysis, which included log-buprenorphine, log-norbuprenorphine and log-lofexidine and two interaction terms (lofexidine and buprenorphine and lofexidine and nor-buprenorphine). As the interaction terms were not statistically significant they were dropped from the model and the sponsor considered univariate analysis for projecting the effects of lofexidine on the QTc interval on-top of buprenorphine.

To assess the appropriateness of this approach, the reviewer evaluated the time-course of lofexidine PK compared to changes in Δ QTcF and Δ HR, which is shown in Figure 8.

Consistent with sponsor's by-time analysis, this analysis did not reveal a difference in $\Delta QTcF$ (lofexidine + buprenorphine vs. buprenorphine) and a decrease in heart rate was observed in the lofexidine + buprenorphine arm (maximum mean ΔHR was -17 bpm). Furthermore, the absence of changes in $\Delta QTcF$ does not support the use of a concentration- QTc model.

Overall, because of the absence of a positive control, the findings of this study only support the absence of a large mean increase in the $QTcF$ interval for lofexidine + buprenorphine vs. buprenorphine.

5.6 ASSESSMENT OF THE DRUG-DRUG INTERACTION STUDY FOR LOFEXIDINE AND NALTREXONE (STUDY LX1-1009)

Study LX1-1009 was a naltrexone DDI study conducted in 24 healthy subjects. Subjects received 2 separate single doses of lofexidine HCl 0.4 mg, one on Day 1 and one on Day 11. Naltrexone was administered QD from Day 4 through Day 13 so that the second lofexidine dose was administered in the presence of steady-state concentrations of naltrexone (50 mg QD) and its metabolite, 6 β -naltrexol. Holter ECG extractions were performed in duplicate from recordings made under resting conditions at predose and 3, 4, and 8 hours postdose on Day 1 and Day 11.

The sponsor evaluated the changes in $\Delta QTcF$ and ΔHR on day 1 (lofexidine single dose) and day 11 (lofexidine single dose after repeat dosing of naltrexone) (b) (4)

(b) (4) this study evaluated a sub-therapeutic dose of lofexidine and did not include a positive control (b) (4)

5.7 EVALUATION OF THE EFFECTS OF LOFEXIDINE IN PATIENTS RECEIVING LOFEXIDINE TO MITIGATE OPIATE WITHDRAWAL (STUDY LX1-3003-1)

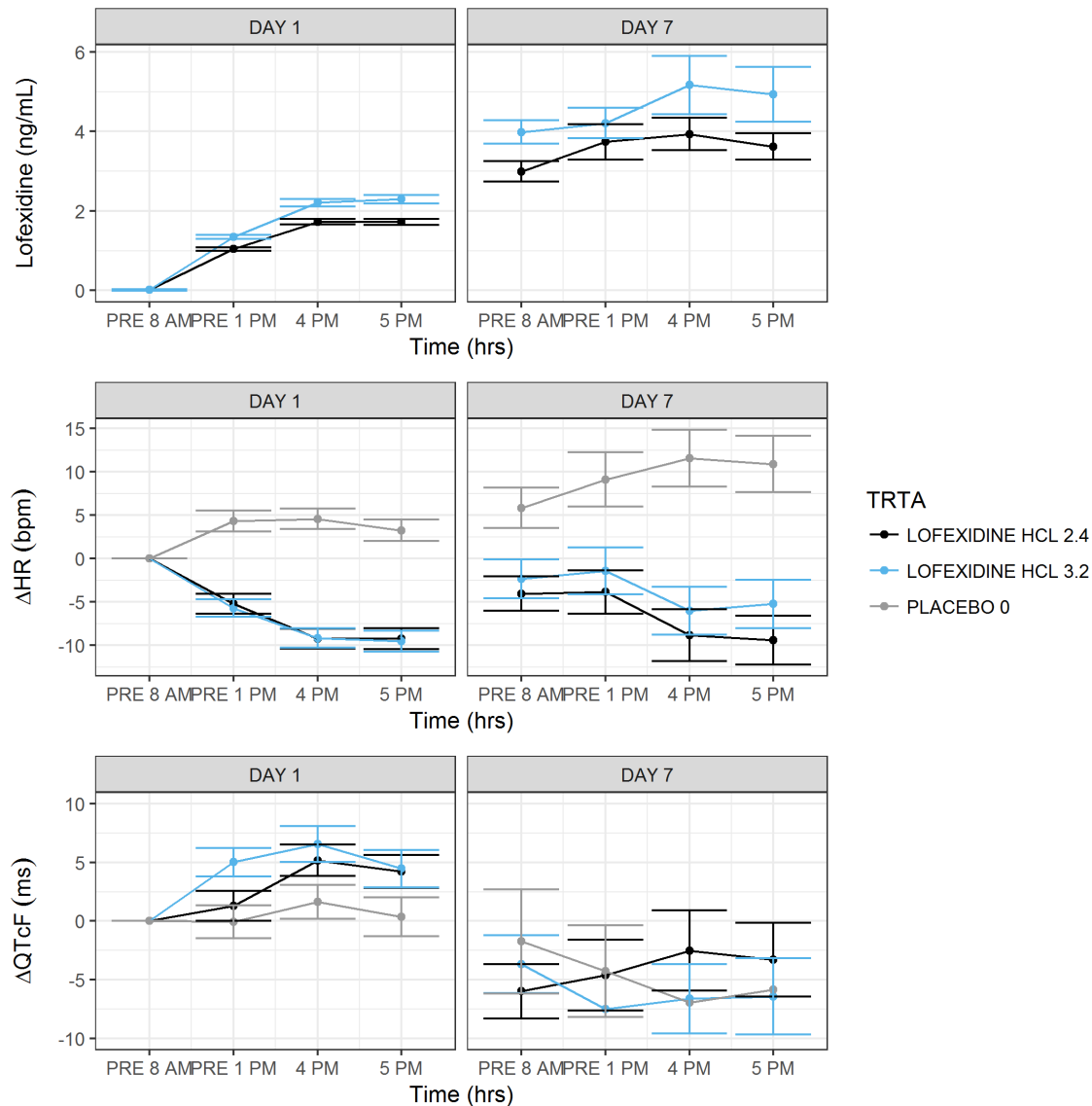
Study LX1-3003-1 was a placebo-controlled efficacy, safety, and dose-response study in 681 subjects undergoing detoxification from short-acting opioids. Subjects were randomized in a 3:3:2 ratio to receive lofexidine HCl 2.4 mg/day (0.6 mg 4 times daily [QID]), lofexidine HCl 3.2 mg/day (0.8 mg QID), or placebo QID. The first part of the study (Days 1-7) comprised an inpatient visit during which subjects received randomized study treatment. During the second part of the study (Days 8-14), all subjects who successfully completed Days 1-7 were eligible to receive open-label, variable-dose lofexidine treatment as determined by the investigator.

The reviewer performed an independent analysis using the PK and ECG data submitted by the sponsor. The reviewer assessed whether the study data supports there are HR and $QTcF$ differences between placebo vs. lofexidine treatments on Day 7 of the study, when lofexidine concentrations were larger than on Day 1. Of note, the reviewer used the pre-dose measurements on day 1 as the baseline, whereas the primary analysis used a different definition. However, the results obtained by the reviewer are comparable to those of the sponsor.

Figure 9 below shows PK and change from baseline ECG time profiles on Day 1 (left panels) when subjects started the treatment (lofexidine 2.4 mg, lofexidine 3.2 mg or placebo) for opioid withdrawal and on Day 7 (right panels) when lofexidine reached

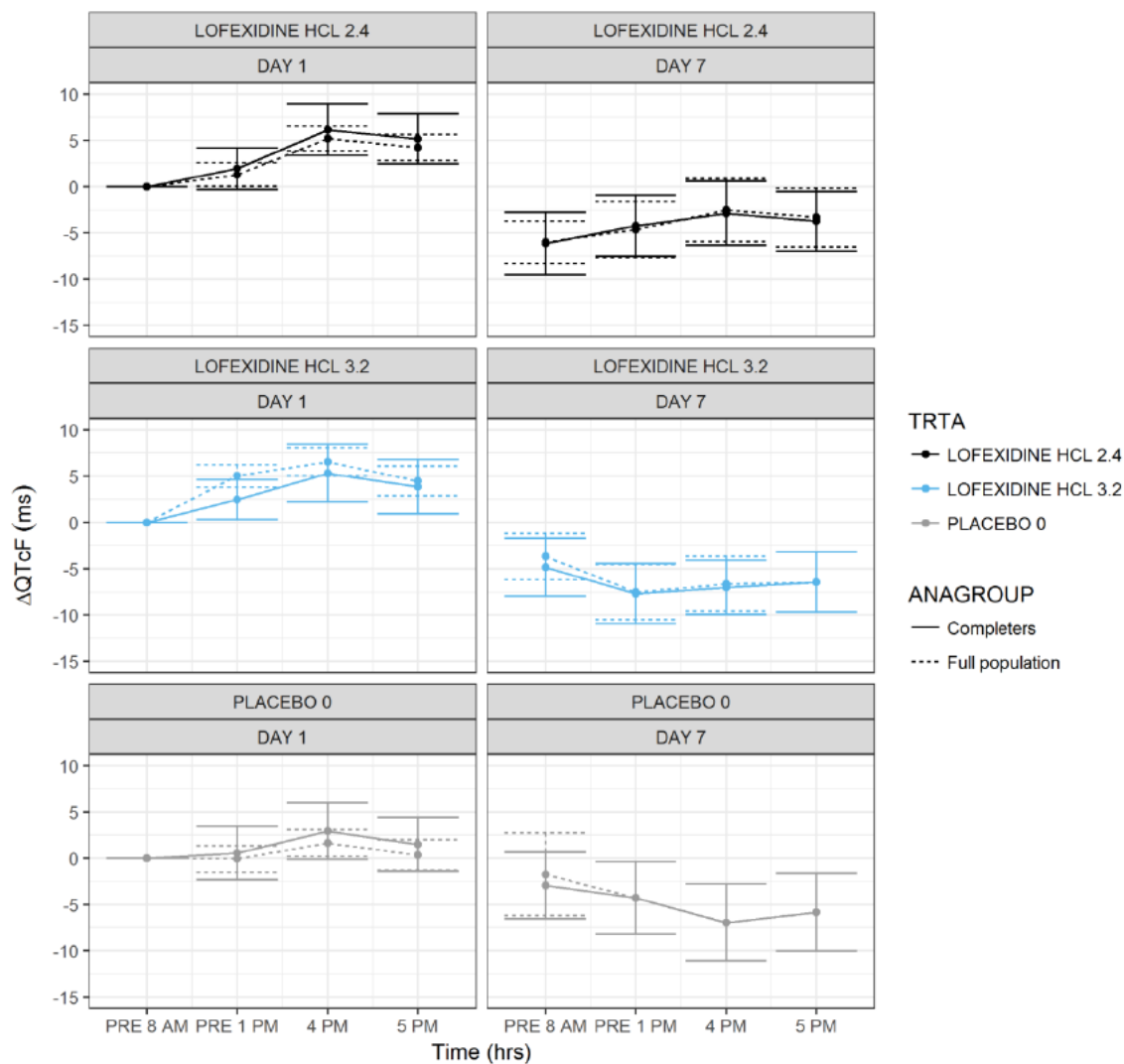
maximum plasma concentration levels. An increase in Δ QTcF was observed on Day 1 for lofexidine 3.2 mg, which was not observed on Day 7 in any of the treatment arms despite the higher lofexidine plasma concentrations (Figure 9). This observation is consistent with the initial analysis performed by the sponsor.

Figure 9: Study LX1-3003-1 lofexidine concentration and changes from baseline for HR (Δ HR) and QTcF (Δ QTcF) per treatment arm, study day and time-point – full population



Of note, there were many drop-outs in this study and a sensitivity analysis was therefore carried out comparing the changes in QTcF for the full population and completers, which is shown in Figure 10. This analysis did not reveal significant differences between these two populations, consistent with the sponsor's sensitivity analysis. Similar results were obtained for heart rate.

Figure 10: Sensitivity analysis to completer status for Δ QTcF



To further explore the relationship between lofexidine pharmacokinetics and changes from baseline in the QTcF interval, the sponsor conducted a post-hoc analysis, which showed a presence of a relationship between lofexidine concentration and Δ QTcF on day 1, but not on day 7. (b) (4)

Moreover, an increase in QTc was observed for patients receiving lofexidine on-top of methadone at steady-state lofexidine exposure (section 5.4).

Overall, the findings of this study do not suggest that lofexidine causes large mean increases in the QTc (i.e., 20 ms).

5.8 SAFETY ASSESSMENT

The reviewer conducted a safety assessment using the “*Integrated Summary of Safety*” datasets focusing on adverse events that are included in the narrow and broad SMQ for “Torsade de pointes/QT prolongation” per MedDRA v18.0. In this analysis, all lofexidine arms (i.e., lofexidine, lofexidine 3.2 mg, lofexidine 2.4 mg, methadone + lofexidine and buprenorphine + lofexidine) were grouped as lofexidine and all arms with placebo were grouped as placebo (i.e., placebo, methadone + placebo and buprenorphine + placebo).

No difference in the frequency of narrow “Torsade de pointes/QT prolongation” adverse events were observed between pooled lofexidine and pooled placebo (Table 7). Of note, all the events captured by the narrow SMQ were cases of QTc prolongation, which in five cases resulted in drug withdrawal or interruption (3 on lofexidine and 2 on placebo) and for one of the lofexidine cases, an adverse event for QTc prolongation was also reported. In contrast to the narrow SMQ results, a difference between pooled lofexidine and pooled placebo was observed for the broad SMQ. The imbalance in observed syncope is likely related to the bradycardia and hypotension caused by lofexidine.

Table 7: Adverse event frequency for narrow and broad torsade de pointes/QT prolongation SMQ

SMQ	Lofexidine (n = 1024)		Placebo (n=345)	
	Events	Patients	Events	Patients
Narrow	6	4	6	5
QTc prolongation	6	4	6	5
Broad	14	11	6	5
Syncope	8	8	0	0
QTc prolongation	6	4	6	5

6 APPENDIX

Please note, that the doses in appendix are expressed as total lofexidine dose.

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Source: IND 47857, SDN 159 ([Link](#)).

Therapeutic dose	0.8 mg QID (3.2 mg daily)	
Maximum tolerated dose	2.0 mg as a single oral dose in normal healthy volunteers. In a pilot QT study (USWM-LX1-1011) a 2.0 mg oral dose was administered to 12 subjects. All experienced disturbing side effects (see below) and the Principal Investigator did not think it was safe to go to a higher dose (especially because of the cardiovascular side effects, hypotension and syncope).	
Principal adverse events	Somnolence, dry mouth, hypotension, dizziness,, nausea, headache, vasovagal syncope, anorexia, diarrhea	
Maximum dose tested	Single Dose	2 mg
	Multiple Dose	1.0 mg QID for 7 days (N=3, withdrawing addict patients) 0.8 mg QID for 5 days (normal healthy volunteers, N=4 remained after a 67% discontinuation rate during dose escalation.)
Exposures Achieved at Maximum Tested Dose	Single Dose	Dose: 2 mg Cmax: 2,968 (16%) pg/mL; AUC _∞ : 70,888 (35%) pg•hr/mL
	Multiple Dose	Dose: 0.8 mg at 8:00, 13:00, 18:00, and 23:00 for 5 days steady-state morning Cmax: 2510 (70%) pg/mL steady-state morning AUC _{0-24h} : 10876 (70%) pg•hr/mL the final dose AUC _∞ : 71508 (71%) pg•hr/mL
Range of linear PK	0.2 to 0.8 mg approximately linear as SD and as MD 1.6 mg and 2.0 mg show linearity as single doses	
Accumulation at steady state	3.1 (58%) with the 0.8 mg QID dosing schedule	
Metabolites	1. 2 O-glucuronides of 2,6-dichlorophenol 2. 2,6-dichlorophenol 3. N- [2'-(2", 6"-dichlorophenoxy) propionyl-1, 2-diaminoethane (the ring-opened analog of lofexidine) 4. 2-(2',6'-dichlorophenoxy)propionic acid 5. Glucuronides and/or sulfate conjugates of #3 and 34 None of the metabolites has been noted to have activity	
Absorption	Absolute/Relative Bioavailability	Oral bioavailability (compared to an IV infusion 0.2 mg) of a 0.4 mg oral dose in a healthy volunteer study population is 65% (preliminary estimate using non-QA'ed data)
	Tmax	• 3.0 (2, 5) h after 0.8 mg SD • 6.0 (3, 12) h after 2 mg SD • Median (range) for metabolites (not known)

Distribution	Vd/F or Vd	• Vz/F=532 L (33%) after 0.4 mg oral [N=11] • Vz=303 L (23%) after 0.2 mg IV [N=11] (measured in healthy volunteers)
	% bound	40% plasma protein bound (spiked plasma in vitro)
Elimination	Route	• Renal elimination is primary, accounting for a mean of 85% (range: 73%-94%) of administered ¹⁴C-labelled dose • 1.5% of administered radiolabel was recovered in the feces
	Terminal t _{1/2}	• 12.5 hr (36%) (2 mg oral SD) • 12.4 hr (30%) (0.8 mg oral SD) • 20.18 hr (31%) (0.8 mg QID x5 days oral MD) • 15.6 hr (12%) for total radioactivity over the interval 12-72 hours post-dose
	CL/F or CL	• CL/F: 29.8 L/hr (35%) (0.4 mg oral SD [N=11]) • CL: 18.1 L/hr (24%) (0.2 mg IV SD [N=11]) (measured in healthy volunteers)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC (Not known)
	Sex	Specify mean changes in C _{max} and AUC (Not known)
	Race	Specify mean changes in C _{max} and AUC (Not known)
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC (Not known)
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC (None completed yet)
	Food Effects	C _{max} : Fasted: 744 pg/mL (24%) Hi Fat: 732 pg/mL (32%) AUC _t : Fasted: 14,150 pg•h/mL (25%) Hi Fat: 14,230 pg•h/mL (30%) AUC _∞ : Fasted: 16,110 pg•h/mL (25%) Hi Fat: 15,860 pg•h/mL (30%) (no food effect when comparing fasting and a high fat breakfast)
	Patient Status	Withdrawing addicts are less sensitive to the cardiovascular effects (hypotension, bradycardia) of lofexidine than healthy volunteers, presumably because of the increased adrenergic tone associated with opiate withdrawal. The cardiovascular sensitivity of opiate addicts on a maintenance opiate dose is not known, but is being assumed to be more like

		healthy volunteers.. Slow upwards titration of the lofexidine dose over several days and regular monitoring of ECG and vital signs following each dose is planned for studies in the maintained addict population. Studies in healthy volunteers suggest that there is not a significant degree of adaptation to the cardiovascular effects of lofexidine with repeated dosing.
Expected High Clinical Exposure Scenario	Worst case scenario with a single dose study will be an approximately 50% increase in peak exposure, assuming the preliminary estimate of absolute bioavailability of approximately 65% oral bioavailability. Cumulative exposure might increase more than that 50% if drug elimination was also slowed, e.g. in renal impairment or hepatic impairment, because lofexidine and its metabolites are cleared almost completely by renal elimination, although only about 11% of the dose is recovered in the urine as parent drug, the rest being the metabolites (the O-glucuronides accounting for the majority of the recovered drug). The cardiovascular effects of hypotension and bradycardia are closely linked to changes in lofexidine plasma concentration, although the sensitivity to these effects (concentration-effect relationship) varies from person to person and is presumed to be linked to the underlying adrenergic tone.	

6.2 OVERVIEW OF ECG MONITORING PER STUDY

Table 8: Studies in healthy volunteers

Study Number (USWM-)	Type of Study	Number of Subjects Who Received Study Medication	Lofexidine HCl dosing	ECGs Centrally Read?	Time from Dose to ECG Measure	ECG Results
<i>Pilot QTc Study</i>						
LX1-1011	Pilot QTc, no placebo control	12	Single-dose oral 2.0 mg and 1.6 mg	Yes	0, 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 16, 22 hours	Mean QTcI and QTcF showed maximal changes from baseline at time of peak lofexidine plasma concentrations, with mean change from baseline ≥ -8 msec for QTcI and ≥ -12 msec for QTcF (Section 3.3.1)
<i>Other Studies in Healthy Subjects</i>						
LX1-1001	Pilot dose-ranging, no placebo control	2	Single-dose IV, 0.2 mg	No	200 min, 10 hours post start of infusion	No clinically significant findings.
LX1-1002	Ascending single- and multiple-dose PK, no placebo control	12	Multiple doses of lofexidine 0.2, 0.4, and 0.8 mg	No	4 hours	No clinically significant findings.
LX1-1003	Mass balance, ADME, absolute BA, no placebo control	12	Single-dose oral 0.4 mg; SD IV 0.228 mg	Yes	0, 3, 4, 8 hours	Increase in QTcF correlated with lofexidine plasma concentration (Section 3.3.2.1).
LX1-1003-1	Repeat mass balance, no placebo control	12	Single-dose oral 0.4 mg	Yes	0, 3, 4, 7, 8 hours	No clinically significant findings (Section 3.3.2.2)
LX1-1004	Food effect, no placebo control	12	Single-dose oral 0.4 mg, fasted/fed	Yes	0, 3, 4, 8 hours	QTcF prolonged by about 9 msec at peak in fasted but not fed (Section 3.3.2.3)
LX-1009	Naltrexone DDI, no placebo control	24	Single-dose oral 0.4 mg, with and without naltrexone 50 mg QD	Yes	0, 3, 4, 8 hours 3.5, 7 hours	No clinically significant findings (Section 3.3.2.4)
LX-1010	Paroxetine DDI (CYP2D6 inhibitor), no placebo control	24	Single-dose oral 0.4 mg with and without paroxetine 40 mg	Yes	0, 3, 4, 8 hours	Negligible effect on QTcF (Section 3.3.2.5)

ADME = absorption, distribution, metabolism, and excretion; BA = bioavailability; DDI = drug-drug-interaction; ECG = electrocardiogram; QTc, heart rate-corrected QT interval; QTcF = heart rate-corrected QT interval (Fridericia's correction); QTcI = heart rate-corrected QT interval (individual correction).

Source: [Integrated Summary of Safety](#), page 4378, Table 30.

Table 9: Studies in special populations

Study Number (USWM-)	Type of Subject (number who received study medication)	Type of Study	Number of Subjects Who Received Lofexidine	Lofexidine HCl dosing	ECGs Centrally Read?	Time from Dose to ECG Measure	QTc Results
LX1-1007	Mild (6), moderate (6), or severe hepatic impairment (6); normal hepatic function (6)	hepatic impairment, no placebo control	24	Single-dose oral 0.4 mg	Yes	0, 3, 4, 8 hours	Moderate increases in QTcF, greatest in subjects with severe hepatic impairment (Section 3.4.1)
LX1-1008	ESRD (8); normal renal function (8)	renal impairment, no placebo control	16	Single-dose oral 0.4 mg	Yes	0, 3, 4, 8 hours	Maximal means Δ QTcF at T _{max} , with mean change from baseline of 22.3 msec in subjects with ESRD and 12.5 msec in subjects with normal renal function (Section 3.4.2)
LX1-1012	Mild (6), moderate (6), and severe (5) renal impairment; normal renal function (6)	renal impairment, no placebo control	23	Single-dose oral 0.4 mg	Yes	0, 3, 4, 8 hours	Small effects on the QTcF in the normal and mild renal impairment groups and larger effects in subjects with moderate or severe renal impairment (Section 3.4.3)

ECG = electrocardiogram; ESRD = end-stage renal disease; QTcF = heart rate-corrected QT interval (Fridericia's correction).

Source: [Integrated Summary of Safety](#), page 4397, Table 44.

Table 10: Opioid-dependent subjects

Study Number (USWM-)	Type of Subject	Type of Study	Number of Subjects Who Received Lofexidine/ Placebo	Lofexidine HCl dosing	ECGs Centrally Read?	Time from Dose to ECG Measure	ECG Results
LX1-1005-1	Receiving methadone maintenance for opioid dependence, no placebo control	Pilot for QTc effects with methadone coadministration	6/0	Multiple oral doses, 1.6 to 3.2 mg/day (0.4 to 0.8 mg QID)	Yes	0, 2, 4 hours	Temporal trend for increase in QTcF (Section 3.2.1)
LX1-1005-2	Receiving methadone maintenance for opioid dependence, placebo control	QTc effects with methadone coadministration	20/7	Multiple-dose oral up to 3.2 mg/day (0.8 mg QID)	Yes	0, 2, 4 hours	Slight increase in QTcF (Section 3.2.1.2.2)
LX-1006	Receiving buprenorphine maintenance for opioid dependence, placebo control	QTc effects with buprenorphine coadministration	24/6	Multiple-dose oral up to 3.2 mg/day (0.8 mg QID)	Yes	0, 2, 4 hours	No significant changes in mean QTcF (Section 3.2.2)
LX1-1013	Receiving buprenorphine maintenance for opioid dependence, no placebo control	Metabolite exposure with buprenorphine administration	10/0	Multiple-dose oral up to 3.2 mg/day (up to 0.8 mg QID)	Yes	0, 3, 4 hours	No significant changes in mean QTcF (Section 3.2.3)

ECG = electrocardiogram; QID = 4 times daily; QTc = heart rate-corrected QT interval; QTcF = heart rate-corrected QT interval (Fridericia's correction); SD = standard deviation.

Source: [Integrated Summary of Safety](#), page 4357, Table 16.

Table 11: Phase 2 studies

Study Number (USWM-)	Type of Subject (number who received study medication)	Type of Study	Number of Subjects Who Received Lofexidine	Lofexidine HCl dosing	Time from Dose to ECG Measure	ECG Results
LX1-2001	Subjects dependent on heroin, morphine, or hydromorphone	3-part, open-label safety	54	1.6 mg (0.8 mg BID); 2.4 mg (1.2 mg BID or 0.8 mg TID) or 4.0 mg/day (1.0 mg QID) for 7 days followed by 3-day taper 3.2 mg/day (0.8 mg QID or 1.6 mg BID) for 5 days	Not stated	Small mean increase in QTc; method of heart rate correction not stated
LX1-2003	Opioid-dependent subjects	Prospective, double-blind safety	14	QD administration Week 1, 0.2 mg Week 2, 0.4 mg Week 3, 0.6 mg Week 4, 0.8 mg Week 5, 1.0 mg Week 6, 1.2 mg Week 7, 1.4 mg Week 8, 1.6 mg	5 h 3, 3.5, 4, 4.5 hours in a subset of subjects	QTc prolongation with methadone coadministration

Source: [Integrated Summary of Safety](#), page 4406, Table 53.

Table 12: Phase 3 studies

Study Number (USWM-)	Type of Subject	Type of Study	Number of Subjects Who Received Lofexidine/ Placebo	Lofexidine HCl dosing	ECGs Centrally Read?	ECG Results
LX1-3003-1	Undergoing withdrawal from short-acting opioids	Placebo-controlled efficacy and safety phase followed by open-label phase	2.4 mg 256, 3.2 mg 255/ 170	Multiple doses of 2.4 mg/day (0.6 mg QID) or 3.2 mg/day (0.8 mg QID) Days 1-7; optional variable dosing Days 8-14	Yes	Small mean increase in QTcF on first day of dosing (Section 3.1.1)
LX1-3002	Undergoing withdrawal from short-acting opioids	Placebo-controlled efficacy and safety	133/128	Multiple doses of 3.2 mg/day (0.8 mg QID) for 5 days	No	No QTcB prolongation observed or other clinically significant changes; however, since there is an HR reduction with lofexidine, the use of QTcB could have masked an effect (Section 3.1.2)
LX1-3001	Undergoing withdrawal from short-acting opioids	Supportive placebo-controlled efficacy and safety	35/33	Multiple doses of 3.2 mg/day for 5 days	No	No effect on QTcB or other ECG parameters; however, since there is an HR reduction with lofexidine, the use of QTcB could have masked an effect (Section 3.1.3)
LX1-3003-2	Undergoing withdrawal from any opioid, including methadone and buprenorphine maintenance treatment	Open-label safety (no placebo control)	286/0	Multiple doses of 3.2 mg/day (0.8 mg QID) with option to lower dose to 2.4 mg/day (0.6 mg QID) for tolerability for 7 to 14 days	Yes	No adverse effect on QTcF or other ECG parameters (Section 3.1.4)

ECG = electrocardiogram; QID = 4 times daily; QTc = heart rate -corrected QT interval (Bazett's correction); QTcF = heart rate-corrected QT interval (Fridericia's correction).

Source: [Integrated Summary of Safety](#), page 4433, Table 2.

6.3 CATEGORICAL ECG OUTLIER TABLES FOR PR AND QRS

Table 13: Number and percentage (%) of subjects within PR interval ranges by absolute values. Safety Population

Population	Study	Treatment	Subjects	200 <= PR < 220 (ms)	PR >= 220 (ms)
Healthy Volunteers	LX1-1002	LFX	12	1 (8.3)	0
Healthy Volunteers	LX1-1003	LFX	12	0	0
Healthy Volunteers	LX1-1003-1	LFX	6	0	1 (16.7)
Healthy Volunteers	LX1-1004	LFX	13	0	0
Methadone maintained	LX1-1005-1	LFX	6	0	0
Methadone maintained	LX1-1005-2	LFX	19	3 (15.8)	0
Methadone maintained	LX1-1005-2	Placebo	7	0	1 (14.3)
Buprenorphine maintained	LX1-1006	LFX	24	3 (12.5)	0
Buprenorphine maintained	LX1-1006	Placebo	6	1 (16.7)	0
Hepatic impairment: Mild	LX1-1007	LFX	5	0	0
Hepatic impairment: Moderate	LX1-1007	LFX	6	1 (16.7)	0
Hepatic impairment: Normal	LX1-1007	LFX	6	1 (16.7)	0
Hepatic impairment: Severe	LX1-1007	LFX	6	1 (16.7)	0
Renal impairment: ESRD	LX1-1008	LFX	8	1 (12.5)	0
Renal impairment: Normal	LX1-1008	LFX	8	0	0
Healthy Volunteers	LX1-1009	LFX	24	5 (20.8)	2 (8.3)
Healthy Volunteers	LX1-1010	LFX	24	1 (4.2)	1 (4.2)
Healthy Volunteers	LX1-1011	LFX	12	0	1 (8.3)
Renal impairment: Mild	LX1-1012	LFX	6	0	0
Renal impairment: Moderate	LX1-1012	LFX	5	0	0
Renal impairment: Normal	LX1-1012	LFX	6	0	0
Renal impairment: Severe	LX1-1012	LFX	5	1 (20.0)	1 (20.0)
Buprenorphine maintained	LX1-1013	LFX	10	0	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	LFX 3.2	35	0	1 (2.9)
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	Placebo	33	1 (3.0)	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	LFX 3.2	134	9 (6.7)	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	Placebo	129	2 (1.6)	1 (0.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 2.4	252	16 (6.3)	5 (2.0)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 3.2	251	9 (3.6)	7 (2.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	Placebo	163	3 (1.8)	2 (1.2)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX OL	148	3 (2.0)	1 (0.7)
Subjects undergoing withdrawal from various treatment scenarios	LX1-3003-2	LFX	286	19 (6.6)	4 (1.4)

Source: Table 2, pages 7-8 in sponsor's response to FDA IR 01-17-18 ([Link](#)).

Table 14: Number and percentage (%) of subjects within QRS interval ranges by absolute values. Safety Population

Population	Study	Treatment	Subjects	110 ≤ QRS < 120 (ms)	QRS ≥ 120 (ms)
Healthy Volunteers	LX1-1002	LFX	12	0	0
Healthy Volunteers	LX1-1003	LFX	12	0	1 (8.3)
Healthy Volunteers	LX1-1003-1	LFX	6	1 (16.7)	0
Healthy Volunteers	LX1-1004	LFX	13	1 (7.7)	0
Methadone maintained	LX1-1005-1	LFX	6	2 (33.3)	0
Methadone maintained	LX1-1005-2	LFX	19	1 (5.3)	1 (5.3)
Methadone maintained	LX1-1005-2	Placebo	7	2 (28.6)	1 (14.3)
Buprenorphine maintained	LX1-1006	LFX	24	6 (25.0)	0
Buprenorphine maintained	LX1-1006	Placebo	6	0	0
Hepatic impairment: Mild	LX1-1007	LFX	5	0	0
Hepatic impairment: Moderate	LX1-1007	LFX	6	0	0
Hepatic impairment: Normal	LX1-1007	LFX	6	0	0
Hepatic impairment: Severe	LX1-1007	LFX	6	0	0
Renal impairment: ESRD	LX1-1008	LFX	8	0	2 (25.0)
Renal impairment: Normal	LX1-1008	LFX	8	1 (12.5)	0
Healthy Volunteers	LX1-1009	LFX	24	1 (4.2)	0
Healthy Volunteers	LX1-1010	LFX	24	8 (33.3)	0
Healthy Volunteers	LX1-1011	LFX	12	1 (8.3)	0
Renal impairment: Mild	LX1-1012	LFX	6	3 (50.0)	0
Renal impairment: Moderate	LX1-1012	LFX	5	0	0
Renal impairment: Normal	LX1-1012	LFX	6	0	0
Renal impairment: Severe	LX1-1012	LFX	5	2 (40.0)	0
Buprenorphine maintained	LX1-1013	LFX	10	3 (30.0)	1 (10.0)
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	LFX 3.2	35	0	1 (2.9)
Subjects undergoing withdrawal from short-acting opioids	LX1-3001	Placebo	33	1 (3.0)	0
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	LFX 3.2	134	8 (6.0)	2 (1.5)
Subjects undergoing withdrawal from short-acting opioids	LX1-3002	Placebo	129	5 (3.9)	1 (0.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 2.4	252	8 (3.2)	2 (0.8)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX 3.2	251	8 (3.2)	3 (1.2)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	Placebo	163	4 (2.5)	1 (0.6)
Subjects undergoing withdrawal from short-acting opioids	LX1-3003-1	LFX OL	148	0	1 (0.7)
Subjects undergoing withdrawal from various treatment scenarios	LX1-3003-2	LFX	286	11 (3.8)	1 (0.3)

Source: Table 3, pages 9-10 in sponsor's response to FDA IR 01-17-18 ([Link](#)).

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02/20/2018

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 6, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 209229
Product Name and Strength:	Lucemyra (lofexidine), 0.18 mg tablet
Product Type:	Single-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	US WorldMeds, LLC
Submission Date:	September 26, 2017
OSE RCM #:	2017-1994
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

We are responding to a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). DAAAP wants us to evaluate the proposed Lucemyra (Lofexidine) labels and labeling. Thus, we reviewed the labels and labeling to identify error prone content and provide comments.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A B
Human Factors Study	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

After conducting a risk assessment, we identified the following concerns with the Prescribing Information:

- The tables for hepatic and renal impairment dose reductions in Section 2.2 and 2.3, respectively, present the total daily dose first. This could be confused as the amount per dose, leading to an overdose. We have seen post-marketing medication errors occur when the total daily dose is presented first and the amount per dose presented second, leading to confusion.^a
- The Applicant uses the abbreviation 'x/day' to signify three times daily or four times daily. To minimize confusion, a footnote should be added to clarify this abbreviation.

We provide recommendations in Section 4.1 to address these issues.

^a Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014;19(25):2-3.

There are no areas of concern from a medication error perspective for the proposed container label, carton labeling, and Patient Product Information.

4 CONCLUSION & RECOMMENDATIONS

Our risk assessment identified areas of concern with the Prescribing Information that can be optimized to minimize confusion. We provide comments in Section 4.1 to address these deficiencies. There are no areas of concern from a medication error perspective for the proposed container label, carton labeling, and Patient Product Information.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information, Section 2.2 and Section 2.3

1. The tables for hepatic and renal impairment dose reductions present the total daily dose first. This could be confused as the amount per dose, leading to an overdose. We have seen post-marketing errors occur when the total daily dose is presented first and the amount per dose presented second, leading to confusion.^b In each cell of the table, we recommend placing the amount per dose first and the maximum daily dose below that. For example:

3 tablets (0.54 mg) 4x/day Max daily dose: 2.16 mg

2. The Sponsor uses the abbreviation 'x/day' to signify three times daily or four times daily in the hepatic and renal impairment dose reduction tables. To minimize confusion, a footnote should be added to clarify this abbreviation. For example:

3 tablets (0.54 mg) 4x/day* Max daily dose: 2.16 mg
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* 4x/day = four times daily

^b Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014;19(25):2-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lucemyra that US WorldMeds submitted on July 28, 2017.

Table 2. Relevant Product Information for Lucemyra	
Initial Approval Date	N/A
Active Ingredient	Lofexidine
Indication	- mitigation of symptoms associated with opioid withdrawal - facilitation of completion of opioid discontinuation treatment.
Route of Administration	Oral
Dosage Form	Tablets
Strength	0.18 mg
Dose and Frequency	Usual Dose: Four tablets four times daily for 7 days. (b) (4) Renal and hepatic impairment require dose reductions based on the severity of impairment as follows: (b) (4) tablets (b) (4) times daily.
How Supplied/Container Closure	(b) (4) count bottle packaged in a carton
Storage	Room temperature

APPENDIX B. N/A - PREVIOUS DMEPA REVIEWS

APPENDIX C. N/A - HUMAN FACTORS STUDY

APPENDIX D. N/A - ISMP NEWSLETTERS

APPENDIX E. N/A - FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

APPENDIX F. N/A - OTHER

APPENDIX G. LABELS AND LABELING

Container Label - 200%



Carton Labeling



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/s/

JAMES H SCHLICK
12/06/2017

OTTO L TOWNSEND
12/07/2017